

Five Steady States in the Agonist-Only Rendall–Sontag Model for the Initiation of T Cell Activation: Certified Examples with Chain Lengths from 651 to 4000

Alper Ferudun*

October 11, 2026

Abstract

Rendall asked, in an abstract on joint work with Sontag (Oberwolfach Report 8/2018), whether the ODE model for the initiation of T cell activation of François, Voisinne, Siggia, Altan-Bonnet and Vergassola has parameter values with more than three steady states. In the form studied by Rendall and Sontag the model is a kinetic proofreading chain $C_0, \dots, C_N$ of receptor complexes with a negative feedback through the phosphatase SHP-1; they proved that its agonist-only case has exactly one positive steady state for $N = 1, 2$ and, for $N = 3$, at most three, and three for suitable parameters. We answer the question for the agonist-only system with the chain length N treated as a free parameter, as in the Oberwolfach abstracts: for $N = 1000$ and explicit positive rational values of all rate constants and totals the system has exactly five positive steady states in one stoichiometric class, all of them non-degenerate. The proof reduces the steady states to the roots, in an explicit interval, of an explicit polynomial of degree $N + 1$, whose sign is evaluated at six rational points in exact integer arithmetic; the exact count is computer-assisted as well (exact arithmetic; all programs and outputs are in the accompanying package). Fourteen further certified parameter points have $N = 651, 652, 653, 655, 660, 680, 690, 700, 2000$ and 4000 . At each of the fifteen points the second and the fourth steady state are unstable; for $N = 1000$ the other three are hyperbolic sinks and these two are saddles (computer-assisted, interval arithmetic). In the other direction we prove that there are at most N positive steady states for odd N and at most $N - 1$ for even N , hence at most three for $N \leq 4$, where the source states the bound five for $N = 4$. For $5 \leq N \leq 650$ nothing is proved: numerical searches found no example and suggest that 651 is the smallest possible N (tested, not proved). The values of N that are biologically motivated in the sources, about 20 or less, are therefore not covered; the parameter windows are extremely thin; and no biological conclusion is drawn. The full model with antagonist and the parameter values of the biological literature are not considered. The method is elementary; a limited literature search found no earlier answer, and no priority is claimed. This is an unrefereed note.

1 Introduction

1.1 The model and the question

François, Voisinne, Siggia, Altan-Bonnet and Vergassola [FVS⁺13] introduced a system of ordinary differential equations for the first minutes of the activation of a T cell, a radical simplification of the model of Altan-Bonnet and Germain [ABG05], and Rendall and Sontag [RS17] studied its qualitative behaviour. We use the system in the form and notation of [RS17, Section 2], and only its *agonist-only case* [RS17, Section 3], without antagonist. The unknowns are the concentration S of the active form

*Mercury Software GmbH. Email: alper@mercurycodelab.com. GitHub: <https://github.com/AlperTheKing>.
Unrefereed preprint. CC BY 4.0.

of the phosphatase SHP-1 and the concentrations $C_0, \dots, C_N$ of the complexes of the T cell receptor with its ligand that carry $0, \dots, N$ phosphate groups; $N \geq 1$ is an integer. With $\Sigma := C_0 + \dots + C_N$ the equations are

$$\dot{S} = \alpha C_1 (S_T - S) - \beta S, \quad (1)$$

$$\dot{C}_0 = \kappa (L_1 - \Sigma) (R - \Sigma) + (b + \gamma S) C_1 - (\phi + \nu_1) C_0, \quad (2)$$

$$\dot{C}_j = \phi C_{j-1} + (b + \gamma S) C_{j+1} - (\phi + b + \gamma S + \nu_1) C_j, \quad 1 \leq j \leq N-1, \quad (3)$$

$$\dot{C}_N = \phi C_{N-1} - (b + \gamma S + \nu_1) C_N. \quad (4)$$

These are equations (1)–(4) of the arXiv version of [RS17] and (2.1)–(2.4) of the journal version, with the antagonist terms L_2 and D_j set to zero. The rate constants $\alpha, \beta, \gamma, \phi, b, \kappa, \nu_1$ and the total amounts L_1 (ligand), R (receptor) and S_T (SHP-1) are positive numbers. A steady state is called *positive* if it lies in the *biologically feasible region*, where $S, C_0, \dots, C_N, S_T - S, R - \Sigma$ and $L_1 - \Sigma$ are positive (Section 2).

What Rendall and Sontag prove. By Theorem 1 of [RS17] (Theorem 3.1 in the journal version; Section 3 in both versions), the agonist-only system has exactly one positive steady state for $N = 1$ and for $N = 2$; for $N = 3$ there are parameters for which it has three positive steady states, and it never has more than three. For larger N the text after that theorem says that a polynomial equation of degree $N + 1$ for S can be derived, that there is no obvious reason why it should not have many positive roots when N is large, and that a simple upper bound for their number is N for odd N and $N + 1$ for even N . The journal version adds one sentence which the arXiv version does not contain: simulations gave three steady states for $N = 5$, and no parameters with more than three were found for any value of N .

The question. In his abstract [Ren18] on this joint work, Rendall reports the three steady states and then writes that whether there are parameters for which “more than three steady states exist is an open question” [Ren18, p. 488]. This is record OWR-15993-009 of the UnsolvedMath collection [ula26], where it is listed as open. The wording of the record is a paraphrase: it speaks of the model “with antigen amount and receptor-unbinding rate as parameters”, which, read alone, may suggest that only L_1 and ν_1 are varied. The sentence of the source is about parameters in general; [Ren18] singles out L and ν as the two key inputs of the response function.

The chain length is a parameter. For $N \leq 3$ the question is answered by [RS17], so it concerns the family of all N . The sources count N among the parameters: [Ren18, p. 488] speaks of the parameter N , and says of a formula containing N that all quantities in it other than L and ν are positive parameters of the ODE system; the earlier abstract [Ren17, p. 1775] introduces N as one parameter of the system, a positive integer; and [RS17, Section 3] announces multistationarity for suitable values of N and of the reaction constants, without regard, at that stage, to biological relevance. We therefore read the question as follows.

Problem 1.1 (Rendall [Ren18, p. 488]). *Are there an integer $N \geq 1$ and positive numbers $\alpha, \beta, \gamma, \phi, b, \kappa, \nu_1, L_1, R, S_T$ such that the system (1)–(4) has more than three steady states in the biologically feasible region?*

1.2 Results

The answer to Problem 1.1 is yes, by explicit parameter points with chain lengths $N \geq 651$; for $5 \leq N \leq 650$, and so for every N that the sources regard as biologically motivated, the question remains open (Section 1.3).

Theorem 1.2 (five steady states for $N = 1000$; computer-assisted, exact integer arithmetic). *Let $N = 1000$ and*

$$\begin{aligned} \alpha = \gamma = \phi = L_1 = R = 1, \quad b = \frac{1}{100}, \quad \kappa = \frac{13}{2\,000\,000}, \quad \nu_1 = \frac{13}{4\,000\,000}, \\ \beta = \frac{343\,447}{2 \cdot 10^{11}}, \quad S_T = \frac{9\,906\,777}{10^7}. \end{aligned} \quad (5)$$

Then the agonist-only system (1)–(4) has exactly five steady states in the biologically feasible region. They have five different values of S , they lie in one stoichiometric compatibility class, and each of them is non-degenerate: the Jacobian of the right-hand side of (1)–(4) is invertible there.

At least five follow from the reduction of Lemma 3.2 and the signs of six integers of about 24 000 bits (Table 1); the exact count and the non-degeneracy follow from exact root counts by two methods (Section 5). Further points show that the chain can be shorter.

Theorem 1.3 (further parameter points; computer-assisted, exact integer arithmetic). *Table 2 lists fourteen further parameter points, with N equal to 651, 652, 653, 655, 660, 680, 690, 700, 2000 or 4000 and with positive rational values of all other parameters. For each of them the system (1)–(4) has exactly five steady states in the biologically feasible region, and all of them are non-degenerate.*

In the opposite direction, Descartes’ rule gives the following bound.

Theorem 1.4 (upper bounds; proved without computation). *Let $N \geq 1$ and let all parameters be positive; $b = 0$ is allowed.*

- (a) *The number of positive steady states of (1)–(4), each counted with its multiplicity as a root of the polynomial P of Lemma 3.2, is odd. It is at most N if N is odd and at most $N - 1$ if N is even.*
- (b) *In particular there is exactly one positive steady state for $N = 1$ and $N = 2$, and there are at most three for $N = 3$ and for $N = 4$.*
- (c) *For $N = 4$ three positive steady states occur, for instance for $\alpha = \gamma = \phi = L_1 = R = 1$, $b = 10^{-3}$, $\nu_1 = 10^{-4}$, $\kappa = 2 \cdot 10^{-4}$, $\beta = \frac{1}{200}$, $S_T = \frac{1999}{1000}$.*

For $N \leq 3$ part (b) is contained in [RS17, Theorem 1]; for $N = 4$ the bound stated in [RS17, Section 3] is five.

Theorem 1.5 (stability). *Let (S, C) be a positive steady state of (1)–(4), let $x = (b + \gamma S)/\phi$ be the corresponding root of the polynomial P of Lemma 3.2, and let J be the Jacobian at (S, C) .*

- (a) (Proved without computation.) *$\text{sign det } J = (-1)^{N+1} \text{sign } P'(x)$. If $P'(x) > 0$, then J has an odd number of positive real eigenvalues, counted with multiplicity; in particular the steady state is unstable.*
- (b) (Computer-assisted, exact arithmetic.) *At each of the fifteen parameter points of Theorems 1.2 and 1.3 the five steady states, ordered by increasing S , have $P'(x) < 0, > 0, < 0, > 0, < 0$. Hence the second and the fourth are unstable.*
- (c) (Computer-assisted, interval arithmetic with directed rounding.) *At the parameter point (5), the Jacobian at each of the five steady states has 1002 real and simple eigenvalues. At the first, third and fifth steady state all of them are negative: these are hyperbolic sinks, hence asymptotically stable. At the second and the fourth exactly one eigenvalue is positive: these are saddles with a one-dimensional unstable manifold.*

Tested, not proved. Numerical searches by three different methods found no parameters with more than three positive steady states for $5 \leq N \leq 650$, and a numerical criterion, evaluated for every integer N from 5 to 660, changes sign between $N = 650$ and $N = 651$ (Section 8). On this evidence 651 is the smallest N with more than three positive steady states; proved is only that it lies between 5 and 651.

1.3 What is answered and what is not

Problem 1.1 asks for the existence of parameters, and the sources count N among them; in this sense Theorem 1.2 answers it. The following limits belong to the result.

- *The system.* Only the agonist-only system (1)–(4) is treated. The full model of [FVS⁺13, RS17] with an antagonist ($L_2 > 0$) is not considered.
- *The chain length.* Five steady states are proved for explicit parameter points with $N = 651, 652, 653, 655, 660, 680, 690, 700, 1000, 2000$ and 4000. For $N \leq 4$ more than three are impossible. For $5 \leq N \leq 650$ nothing is proved; searches found no example (tested only). The sources regard much smaller values as biologically motivated: the arXiv version of [RS17] says in Section 2 that a biologically reasonable N could be as large as 20 and that $N = 9$ in the model of [ABG05]; the journal version speaks in its introduction of 20 phosphorylation sites of potential importance, of $N = 5$ in the simulations of [FVS⁺13], and of nine sites in the model of [ABG05]. These values of N are not covered by our examples.
- *The parameter values.* The windows are extremely thin. At the point (5) the five steady states persist, numerically, only while S_T changes by less than a relative amount of $7 \cdot 10^{-7}$, or β by less than $7 \cdot 10^{-5}$; the five values of S differ by one per cent; and the eigenvalues that decide the stability are of order $10^{-8}\phi$. At the point with $N = 651$ the window of S_T has relative width 10^{-13} . The parameter values of the biological literature are not considered, and no biological conclusion is drawn.
- *Credits and priority.* The model, the question and the results for $N \leq 3$ are due to the authors named above. The method, a reduction to one polynomial and the exact evaluation of signs, is elementary. A limited literature search found no earlier answer; this is not a proof of novelty, and no priority is claimed. What was read and what was not is said in the paragraph “Scope and priority” of Section 10.

2 The model

We recall the setting of [RS17, Section 2]. A ligand binds to a receptor with rate constant κ and forms C_0 ; C_j is phosphorylated to C_{j+1} with rate constant ϕ , and C_{j+1} is dephosphorylated to C_j with rate $b + \gamma S$ (basal rate constant b , rate constant γ for active SHP-1); every complex dissociates with rate constant ν_1 ; SHP-1 is activated by C_1 with rate constant α and deactivated with rate constant β . All rate constants are assumed positive. With mass action kinetics this gives a system for $S, C_0, \dots, C_N$ and the concentrations of free ligand, free receptor and inactive SHP-1, whose conservation laws are printed in the journal version of [RS17]; in the agonist-only case they are

$$\Sigma + L_{1,U} = L_1, \quad \Sigma + R_U = R, \quad S + S_I = S_T,$$

where $L_{1,U}$, R_U and S_I are the concentrations of unbound ligand, unbound receptor and inactive SHP-1. Eliminating these three variables gives (1)–(4). The totals L_1 , R , S_T are therefore parameters of

(1)–(4), and fixing them means fixing a stoichiometric compatibility class of the mass action system. For $N = 1$ there are no equations (3).

The *biologically feasible region* is the set of all $(S, C_0, \dots, C_N)$ for which $S, C_0, \dots, C_N, S_T - S, R - \Sigma$ and $L_1 - \Sigma$ are positive; it corresponds to positive concentrations in the system before the elimination. By [RS17, Lemma 1] (Lemma 2.1 in the journal version) every steady state in the closure of this region lies in the region, and by the argument that follows that lemma at least one exists. We do not use these two facts. A *positive steady state* is a zero of the right-hand side of (1)–(4) in the biologically feasible region; steady states are counted for fixed values of N and of the ten other parameters.

3 The reduction to one polynomial

3.1 Two families of polynomials

For a number $\nu > 0$ define polynomials c_j, t_j in x , $0 \leq j \leq N$, by

$$c_N = t_N = 1, \quad c_{j-1} = x c_j + \nu t_j, \quad t_{j-1} = t_j + c_{j-1} \quad (j = N, N-1, \dots, 1). \quad (6)$$

Lemma 3.1. (a) c_j and t_j have degree $N - j$ and leading coefficient 1, and all their coefficients of $x^0, \dots, x^{N-j}$ are positive. (b) $t_j = c_j + c_{j+1} + \dots + c_N$. (c) $c_j(x) > 0$ and $t_j(x) > 0$ for $x \geq 0$, and the functions c_1, t_0, c'_1, t'_0 are non-negative and non-decreasing on $[0, \infty)$.

Proof. (a) By downward induction on j . If the statement holds for j , then $x c_j$ has positive coefficients of $x^1, \dots, x^{N-j+1}$, the highest being 1, and νt_j has positive coefficients of $x^0, \dots, x^{N-j}$; so the statement holds for c_{j-1} , and then for $t_{j-1} = t_j + c_{j-1}$. (b) is an induction on (6), and (c) follows from (a). $\square$

3.2 The reduction

The quadratic polynomial $q(s) = \kappa(L_1 - s)(R - s) - \nu_1 s$ has a positive leading coefficient, $q(0) = \kappa L_1 R > 0$ and $q(m) = -\nu_1 m < 0$ for $m := \min\{L_1, R\}$. Hence q has exactly one root Σ^* in $(0, m)$, and its other root is larger than m . Put

$$\nu := \frac{\nu_1}{\phi}, \quad x_0 := \frac{b}{\phi}, \quad X := \frac{b + \gamma S_T}{\phi}, \quad \rho := \frac{\beta}{\alpha \Sigma^*}, \quad (7)$$

and, with the polynomials (6) for this ν ,

$$P(x) := c_1(x) (X - x) - \rho (x - x_0) t_0(x). \quad (8)$$

P has degree $N + 1$ and leading coefficient $-\rho$.

Lemma 3.2 (reduction). *Let $N \geq 1$, let all parameters be positive, or let $b = 0$ and all others be positive. The map $(S, C) \mapsto x = (b + \gamma S)/\phi$ is a bijection from the set of positive steady states of (1)–(4) onto the set of roots of P in the open interval (x_0, X) . The steady state that belongs to a root x is*

$$S = \frac{\phi x - b}{\gamma}, \quad C_j = \Sigma^* \frac{c_j(x)}{t_0(x)} \quad (0 \leq j \leq N), \quad \text{and it has } \Sigma = \Sigma^*. \quad (9)$$

Moreover $P(x_0) > 0 > P(X)$, so the number of roots of P in (x_0, X) , counted with multiplicity, is odd.

Proof. Write $y := b + \gamma S$ and introduce the net fluxes $F_j := \phi C_{j-1} - y C_j$ for $1 \leq j \leq N$. The right-hand sides of (2), (3) and (4) are

$$\kappa(L_1 - \Sigma)(R - \Sigma) - F_1 - \nu_1 C_0, \quad F_j - F_{j+1} - \nu_1 C_j \quad (1 \leq j \leq N-1), \quad F_N - \nu_1 C_N, \quad (10)$$

as one sees by inserting the definition of F_j . Put $T_j := C_j + \dots + C_N$.

From a steady state to a root. Let (S, C) be a positive steady state; then $y > 0$. The last expression in (10) vanishes, so $F_N = \nu_1 C_N = \nu_1 T_N$; the middle ones vanish, so $F_j = F_{j+1} + \nu_1 C_j$, and by downward induction $F_j = \nu_1 T_j$ for $1 \leq j \leq N$. With $x = y/\phi$ this reads

$$C_{j-1} = x C_j + \nu T_j, \quad T_{j-1} = T_j + C_{j-1} \quad (1 \leq j \leq N). \quad (11)$$

Comparing with (6), $C_j = \theta c_j(x)$ and $T_j = \theta t_j(x)$ for all j , where $\theta := C_N > 0$. The first expression in (10) vanishes and $F_1 + \nu_1 C_0 = \nu_1(T_1 + C_0) = \nu_1 \Sigma$, so $q(\Sigma) = 0$; since $0 < \Sigma < m$ in the feasible region, $\Sigma = \Sigma^*$. Hence $\theta t_0(x) = T_0 = \Sigma^*$ and $C_j = \Sigma^* c_j(x)/t_0(x)$. Finally $S = \phi(x - x_0)/\gamma$ and $S_T - S = \phi(X - x)/\gamma$, so that the right-hand side of (1) is

$$\alpha C_1(S_T - S) - \beta S = \frac{\phi \alpha \Sigma^*}{\gamma} \cdot \frac{P(x)}{t_0(x)}. \quad (12)$$

It vanishes, so $P(x) = 0$; and $0 < S < S_T$ means $x_0 < x < X$.

From a root to a steady state. Let $x \in (x_0, X)$ and define S and C_j by (9). Then $0 < S < S_T$, $y = \phi x$, and $C_j > 0$ by Lemma 3.1(c). By Lemma 3.1(b), $T_j = \Sigma^* t_j(x)/t_0(x)$; so $\Sigma = T_0 = \Sigma^* \in (0, m)$, whence $R - \Sigma > 0$ and $L_1 - \Sigma > 0$, and (11) holds by (6), that is, $F_j = \nu_1 T_j$ for $1 \leq j \leq N$. Then the three expressions in (10) are $\nu_1 \Sigma^* - \nu_1 T_1 - \nu_1 C_0 = 0$ (because $q(\Sigma^*) = 0$), $\nu_1(T_j - T_{j+1} - C_j) = 0$ and $\nu_1(T_N - C_N) = 0$. So (2)–(4) hold for every $x \in (x_0, X)$, and by (12) equation (1) holds if and only if $P(x) = 0$.

The two constructions are inverse to each other. Finally $P(x_0) = c_1(x_0)(X - x_0) > 0$ and $P(X) = -\rho(X - x_0)t_0(X) < 0$ by Lemma 3.1(c). $\square$

The second half of the proof shows more than was needed. For every S with $b + \gamma S \geq 0$ put $x = (b + \gamma S)/\phi$ and $C_j(S) := \Sigma^* c_j(x)/t_0(x)$. Then $(S, C(S))$ satisfies (2)–(4), and the first half shows that, for this S , it is the only solution of these equations with all $C_j > 0$ and $\Sigma < m$. The positive steady states are the points $(S, C(S))$ with $0 < S < S_T$ and $f(S) = 0$, where

$$f(S) := \alpha C_1(S)(S_T - S) - \beta S = \frac{\phi \alpha \Sigma^*}{\gamma} \cdot \frac{P(x)}{t_0(x)}, \quad x = \frac{b + \gamma S}{\phi}. \quad (13)$$

Remark 3.3 (comparison with the polynomials of the source). As a check of the normalisation, the polynomial $\phi^N [\beta S t_0(x) - \alpha \Sigma^* c_1(x)(S_T - S)]$, $x = (b + \gamma S)/\phi$, which is $-P$ up to a positive factor, was compared with the polynomials printed in [RS17, Section 3]. For $N = 1$ it is the quadratic given there, (3.15) in the journal version, and for $N = 2$ it is the cubic given there. For $N = 3$ the coefficients a_0, a_2, a_4 of the quartic agree identically, and a_1, a_3 agree for $\gamma = \phi = 1$, the values of the example in [RS17]; for general γ and ϕ three terms of the printed a_1 and a_3 differ from ours by a factor γ or ϕ (both versions of [RS17]; the comparison is in the package), which affects neither the example nor the sign argument nor Theorem 1 of [RS17]. For the example given after that theorem ($N = 3$, $\alpha = \beta = \gamma = \phi = L_1 = R = 1$, $S_T = 10$, $\kappa = 2 \cdot 10^{-4}$, $\nu_1 = 10^{-4}$, and $b = 0$ as in the preceding proof and in the caption of Figure 2 there) P has exactly three roots in $(x_0, X) = (0, 10)$, and (9) gives the three steady states printed in [RS17] to all four decimals.

3.3 The Jacobian

Order the unknowns as $(S; C_0, \dots, C_N)$ and write the Jacobian of the right-hand side of (1)–(4) in block form,

$$J = \begin{pmatrix} J_{SS} & J_{SC} \\ J_{CS} & J_{CC} \end{pmatrix}, \quad J_{SS} = -\alpha C_1 - \beta, \quad J_{CC} \in \mathbb{R}^{(N+1) \times (N+1)}.$$

Lemma 3.4 (determinant of the Jacobian). *Let (S, C) be a positive steady state, $x = (b + \gamma S)/\phi$, and $\kappa' := \kappa(L_1 + R - 2\Sigma^*) > 0$.*

- (a) *All $N + 1$ eigenvalues of J_{CC} are real and negative. In particular $\det J_{CC} = (-1)^{N+1}$.*
- (b) *$\det J = \det J_{CC} \cdot f'(S)$ and $f'(S) = \alpha \Sigma^* P'(x)/t_0(x)$. Hence $\text{sign } \det J = (-1)^{N+1} \text{sign } P'(x)$, and the steady state is non-degenerate if and only if x is a simple root of P .*
- (c) *$-(\nu_1 + \kappa')$ is an eigenvalue of J , and $\text{tr } J < 0$.*

Proof. (a) Let $y = b + \gamma S$. Differentiating (2)–(4) with respect to the C_k gives $J_{CC} = A - \kappa' e_0 \mathbf{1}^\top$, where e_0 is the first unit vector, $\mathbf{1} = (1, \dots, 1)^\top$, and A is the tridiagonal matrix with diagonal $-(\phi + \nu_1)$, $-(\phi + y + \nu_1)$, $\dots$, $-(\phi + y + \nu_1)$, $-(y + \nu_1)$, with all entries above the diagonal equal to y and all entries below it equal to ϕ . Here $\kappa' = \kappa(L_1 + R - 2\Sigma)$ at $\Sigma = \Sigma^*$, and $\kappa' > 0$ because $\Sigma^* < \min\{L_1, R\}$. Every column of A sums to $-\nu_1$, that is, $\mathbf{1}^\top A = -\nu_1 \mathbf{1}^\top$. The matrix A is similar to a symmetric matrix, by conjugation with the diagonal matrix with entries $(\phi/y)^{j/2}$; so its eigenvalues are real. They are at most $-\nu_1$: if $v^\top A = \lambda v^\top$ with $v \neq 0$ and $|v_j|$ is maximal, then $(\lambda - A_{jj})v_j = \sum_{i \neq j} v_i A_{ij}$, hence $|\lambda - A_{jj}| \leq \sum_{i \neq j} A_{ij} = -\nu_1 - A_{jj}$ and $\lambda \leq -\nu_1$. For λ outside the spectrum of A we have $\mathbf{1}^\top (\lambda - A)^{-1} = (\lambda + \nu_1)^{-1} \mathbf{1}^\top$, and the formula $\det(M + uw^\top) = \det M \cdot (1 + w^\top M^{-1}u)$ gives

$$\det(\lambda - J_{CC}) = \det(\lambda - A) \left(1 + \frac{\kappa'}{\lambda + \nu_1} \right), \quad \text{that is,} \quad (\lambda + \nu_1) \det(\lambda - J_{CC}) = (\lambda + \nu_1 + \kappa') \det(\lambda - A)$$

as polynomials in λ . Since $-\nu_1$ is an eigenvalue of A , the eigenvalues of J_{CC} are $-(\nu_1 + \kappa')$ and the eigenvalues of A with one copy of $-\nu_1$ removed. All are negative.

(b) By the remark after Lemma 3.2, the right-hand sides of (2)–(4) vanish at $(S', C(S'))$ for all S' near S , and $C(S) = C$. Differentiating at $S' = S$ gives $J_{CS} + J_{CC}C'(S) = 0$, and differentiating $f(S') = \alpha C_1(S')(S_T - S') - \beta S'$ gives $f'(S) = J_{SS} + J_{SC}C'(S) = J_{SS} - J_{SC}J_{CC}^{-1}J_{CS}$. This is the Schur complement of J_{CC} in J , so $\det J = \det J_{CC} \cdot f'(S)$. By (13) and $P(x) = 0$, $f'(S) = \alpha \Sigma^* P'(x)/t_0(x)$.

(c) The S -derivatives of the right-hand sides of (2)–(4) are γC_1 , $\gamma(C_{j+1} - C_j)$ and $-\gamma C_N$; their sum is zero, so $\mathbf{1}^\top J_{CS} = 0$. Together with $\mathbf{1}^\top J_{CC} = -(\nu_1 + \kappa') \mathbf{1}^\top$ this shows that $(0; \mathbf{1}^\top)$ is a left eigenvector of J for the eigenvalue $-(\nu_1 + \kappa')$. The trace is negative because $J_{SS} < 0$ and, by (a), $\text{tr } J_{CC} < 0$. $\square$

4 Two ways of counting roots exactly

Both methods are elementary. The first uses only that c_1 , t_0 and their derivatives are monotone; the second is Descartes' rule of signs after a change of variable, a classical device for the isolation of real roots.

Lemma 4.1 (monotone enclosures). *Let $\nu > 0$, $\rho > 0$, $0 \leq x_0 < X$, and let P be given by (8). For $x_0 \leq u < v \leq X$ and all $x \in [u, v]$,*

$$c_1(u)(X - v) - \rho(v - x_0)t_0(v) \leq P(x) \leq c_1(v)(X - u) - \rho(u - x_0)t_0(u), \quad (14)$$

$$D^-(u, v) \leq P'(x) \leq D^+(u, v), \quad (15)$$

where

$$\begin{aligned} D^-(u, v) &:= c'_1(u)(X - v) - c_1(v) - \rho t_0(v) - \rho(v - x_0)t'_0(v), \\ D^+(u, v) &:= c'_1(v)(X - u) - c_1(u) - \rho t_0(u) - \rho(u - x_0)t'_0(u). \end{aligned}$$

Consequently:

- (i) if the left-hand side of (14) is positive or the right-hand side is negative, P has no root in $[u, v]$;
- (ii) if $|P(\frac{u+v}{2})| > \frac{v-u}{2} \max\{|D^-(u, v)|, |D^+(u, v)|\}$, P has no root in $[u, v]$;
- (iii) if $D^-(u, v) > 0$ or $D^+(u, v) < 0$, then P is strictly monotone on $[u, v]$: it has exactly one root in (u, v) , a simple one, if $P(u)P(v) < 0$, and no root in $[u, v]$ if $P(u)P(v) > 0$.

Proof. $P'(x) = c'_1(x)(X - x) - c_1(x) - \rho t_0(x) - \rho(x - x_0)t'_0(x)$. On $[u, v]$ the factors $X - x$ and $x - x_0$ are non-negative and monotone, and by Lemma 3.1(c) so are c_1 , t_0 , c'_1 , t'_0 . Bounding each product by the product of the bounds of its factors gives (14) and (15). (i) and (iii) are immediate, and (ii) follows from the mean value theorem. $\square$

Remark 4.2 (directed rounding). The numbers $c_1(u)$, $t_0(u)$, $c'_1(u)$, $t'_0(u)$ at a rational point $u \geq 0$ are obtained from (6) and from its derivative, $c'_N = t'_N = 0$, $c'_{j-1} = c_j + x c'_j + \nu t'_j$, $t'_{j-1} = t'_j + c'_{j-1}$, by additions and multiplications of non-negative numbers. If every product is rounded down to a multiple of 2^{-p} , the results are lower bounds, and if every product is rounded up, upper bounds. (14), (15) and (i)–(iii) remain valid if in every lower bound the exact values are replaced by lower bounds where they enter with a positive sign and by upper bounds where they enter with a negative sign, and conversely in every upper bound. In this form Lemma 4.1 needs integer arithmetic only.

Lemma 4.3 (Descartes' rule of signs). *Let $T(z) = \sum_{k=0}^n a_k z^k$ be a real polynomial with $a_0 \neq 0 \neq a_n$, let $V(T)$ be the number of sign changes in the sequence of its non-zero coefficients, and $Z(T)$ the number of its positive roots, counted with multiplicity. Then $Z(T) \leq V(T)$, and $V(T) - Z(T)$ is even.*

Proof. This is classical; we include a proof. *Parity.* T changes sign at a positive root exactly if its multiplicity is odd; so $Z(T)$ is even if and only if $a_0 = T(0)$ and a_n , the sign of $T(z)$ for large z , have the same sign. $V(T)$ is even under the same condition. *Inequality,* by induction on n ; for $n = 0$ both numbers are zero. Let $n \geq 1$ and let $m \geq 1$ be the smallest index with $a_m \neq 0$. Then $T'(z) = z^{m-1}T_1(z)$ with $T_1(z) = \sum_{k \geq m} k a_k z^{k-m}$, a polynomial of degree $n - m$ with non-zero constant term, whose coefficients have the signs of $a_m, \dots, a_n$; so $V(T_1) = V(T)$ if $a_0 a_m > 0$ and $V(T_1) = V(T) - 1$ if $a_0 a_m < 0$. By Rolle's theorem $Z(T_1) = Z(T') \geq Z(T) - 1$: a root of multiplicity μ of T is a root of multiplicity $\mu - 1$ of T' , and between two consecutive positive roots of T there is a root of T' . With the induction hypothesis, $Z(T) \leq V(T_1) + 1$. If $a_0 a_m < 0$ this is $Z(T) \leq V(T)$. If $a_0 a_m > 0$ it is $Z(T) \leq V(T) + 1$, and equality is excluded by the parity. $\square$

Lemma 4.4 (Descartes' rule on an interval). *Let p be a real polynomial of degree at most n , let $a < b$ be real numbers with $p(a)p(b) \neq 0$, and let $\text{var}(p; a, b)$ be the number of sign changes in the sequence of the non-zero coefficients of*

$$T(z) := (z + 1)^n p\left(\frac{az + b}{z + 1}\right).$$

Then the number of roots of p in (a, b) , counted with multiplicity, is at most $\text{var}(p; a, b)$ and differs from it by an even number. In particular p has no root in (a, b) if $\text{var}(p; a, b) = 0$, and exactly one root in (a, b) , a simple one, if $\text{var}(p; a, b) = 1$.

Proof. The map $z \mapsto \frac{az+b}{z+1} = a + \frac{b-a}{z+1}$ is a bijection from $(0, \infty)$ onto (a, b) . T is a polynomial of degree n with $T(0) = p(b) \neq 0$ and leading coefficient $p(a) \neq 0$. If $r \in (a, b)$ is a root of p of multiplicity k , write $p(x) = (x-r)^k g(x)$ with $g(r) \neq 0$ and $z_r := (b-r)/(r-a) > 0$; then $\frac{az+b}{z+1} - r = \frac{(a-r)(z-z_r)}{z+1}$, so $T(z) = (a-r)^k (z-z_r)^k \cdot (z+1)^{n-k} g\left(\frac{az+b}{z+1}\right)$, where the last factor is a polynomial that does not vanish at z_r . Hence the positive roots of T correspond to the roots of p in (a, b) , with the same multiplicities, and Lemma 4.3 for T gives the claim. $\square$

5 Five steady states

5.1 Proof of Theorem 1.2

Step 1: the reduced data. All ten numbers in (5) are positive. The equation $q(s) = 0$ reads $2(1-s)^2 = s$ and has the roots $\frac{1}{2}$ and 2; so $\Sigma^* = \frac{1}{2}$, and by (7)

$$\nu = \frac{13}{4\,000\,000}, \quad x_0 = \frac{1}{100}, \quad X = \frac{10\,006\,777}{10^7}, \quad \rho = 2\beta = \frac{343\,447}{10^{11}}.$$

Step 2: at least five. For a rational point $x = a/Q$, where Q is also a denominator of $\nu = n/Q$, the integers $\hat{c}_j := Q^{N-j} c_j(x)$ and $\hat{t}_j := Q^{N-j} t_j(x)$ satisfy, by (6),

$$\hat{c}_N = \hat{t}_N = 1, \quad \hat{c}_{j-1} = a \hat{c}_j + n \hat{t}_j, \quad \hat{t}_{j-1} = Q \hat{t}_j + \hat{c}_{j-1}, \quad Q^N P(x) = Q \hat{c}_1 (X-x) - \rho (x-x_0) \hat{t}_0. \quad (16)$$

This determines the sign of $P(x)$ by integer arithmetic alone. At the six points of Table 1 the signs are $+, -, +, -, +, -$. The points increase from x_0 to X , so by the intermediate value theorem P has a root in each of the five open intervals between consecutive points. By Lemma 3.2 these five roots are five positive steady states with five different values of S . All have the same L_1 , R , S_T , so they lie in one stoichiometric compatibility class.

x	$\frac{1}{100} = x_0$	$\frac{197}{200}$	$\frac{1977}{2000}$	$\frac{9913}{10\,000}$	$\frac{9931}{10\,000}$	$\frac{10\,006\,777}{10^7} = X$
$S = x - \frac{1}{100}$	0	0.975	0.9785	0.9813	0.9831	$0.9906777 = S_T$
sign of $P(x)$	+	−	+	−	+	−
$\psi(x)$	1	$-2.27 \cdot 10^{-5}$	$1.48 \cdot 10^{-5}$	$-1.66 \cdot 10^{-5}$	$2.19 \cdot 10^{-5}$	−1

Table 1: The six exact signs for the parameter point (5); the integers $\hat{c}_1, \hat{t}_0$ of (16) have 21 892 to 24 265 bits. The last row is for orientation only: the normalised balance $\psi := (A - B)/(A + B)$, rounded, where $A := c_1(x)(X - x)$, $B := \rho(x - x_0)t_0(x)$ and $P = A - B$.

Step 3: exactly five, all simple. We give two independent certificates; each was computed by three programs (Table 4).

Certificate I (Descartes). The integer coefficients of a positive multiple of P are computed from (6); the degree is 1001 and the coefficients have up to 21 975 bits. For the ten consecutive intervals (a, b) with end points

$$\frac{1}{100}, \quad \frac{9}{10}, \quad \frac{97}{100}, \quad \frac{49}{50}, \quad \frac{197}{200}, \quad \frac{1977}{2000}, \quad \frac{9913}{10\,000}, \quad \frac{9931}{10\,000}, \quad \frac{199}{200}, \quad \frac{499}{500}, \quad X$$

the numbers $\text{var}(P; a, b)$ of Lemma 4.4, computed exactly, are

$$0, 0, 0, 1, 1, 1, 1, 1, 0, 0,$$

and P does not vanish at the end points. By Lemma 4.4, P has exactly five roots in (x_0, X) , one in each of the five intervals between $\frac{49}{50}$ and $\frac{199}{200}$, and all are simple.

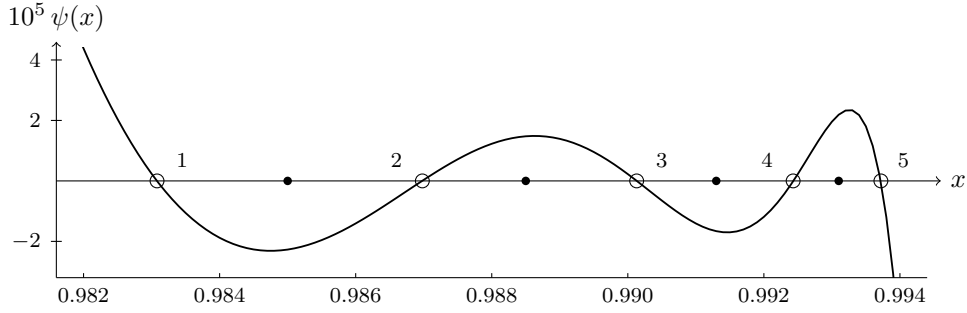


Figure 1: The normalised balance ψ of Table 1 for the point (5), computed exactly at the multiples of 10^{-4} and joined by segments. Filled dots: the four interior test points. Circles: the five roots. The figure illustrates the proof and is not part of it.

Certificate II (enclosures). The interval $[x_0, X]$ is divided into finitely many closed intervals with rational end points, by repeated bisection, until each of them is closed by one of the criteria (i), (ii), (iii) of Lemma 4.1, in the rounded form of Remark 4.2 with $p = 256$; in case (iii) the signs of P at both end points are certified from the enclosures as well. The program of this note needs 939 intervals: 910 of them contain no root, and 29 are intervals of monotonicity, of which five contain exactly one root and 24 none. (The program of verification run B, which works in the variable S , needs 979; that of the third verification run, which starts from the single interval $[x_0, X]$, needs 934, and for Certificate I it found a subdivision into twelve intervals of its own.) So P has exactly five roots in $[x_0, X]$, all simple, and P' has the signs $-, +, -, +, -$ at them. In terms of $S = x - \frac{1}{100}$ the roots lie in

$$\begin{aligned} (0.9730770, 0.9730796), \quad (0.9769764, 0.9769771), \quad (0.9801317, 0.9801321), \\ (0.9824332, 0.9824336), \quad (0.9837152, 0.9837166). \end{aligned} \tag{17}$$

By Lemma 3.2 there are exactly five positive steady states, and by Lemma 3.4(b) each of them is non-degenerate. $\square$

Remark 5.1 (numerical description of the five steady states). The following numbers are not used in any proof. They were computed with 60 to 100 digits by three programs, which agree in the digits shown. The five steady states have

$$S \approx 0.973078759, \quad 0.976976484, \quad 0.980131721, \quad 0.982433429, \quad 0.983715309,$$

$\Sigma = \frac{1}{2}$ and all coordinates C_j larger than $8 \cdot 10^{-5}$; the residuals of all 1002 equations are below 10^{-100} in the computation with 100 digits. The largest eigenvalues of the Jacobian are $-7.38 \cdot 10^{-8}$, $+2.91 \cdot 10^{-8}$, $-2.33 \cdot 10^{-8}$, $+2.77 \cdot 10^{-8}$ and $-6.90 \cdot 10^{-8}$, and the next one is $-(\nu_1 + \kappa') = -9.75 \cdot 10^{-6}$ at each state, in accordance with Lemma 3.4(c).

The windows are thin. With the other reduced parameters fixed, the five roots persist for X in an interval of relative length $6.6 \cdot 10^{-7}$ and for ρ in an interval of relative length $6.4 \cdot 10^{-5}$; in the original parameters these are windows for S_T and for β . The point is also tuned in N : with the reduced parameters of Step 1 and a chain of length N' in place of 1000, a floating-point count for 22 values of N' gives five roots only for $N' = 999$ and 1000, three for the other tested values from 900 to 1010, and one for those up to 850 and from 1025 on; for the thirteen of these values from 850 to 1050 the third verification run confirmed the counts exactly, by Lemma 4.1. Since the six signs of Table 1 are strict and P depends continuously on the parameters, at least five positive steady states exist for all parameters in a neighbourhood of (5), for $N = 1000$; by the above this neighbourhood is small.

5.2 Further parameter points: proof of Theorem 1.3

Table 2 lists fourteen further points. All of them have $\alpha = \gamma = \phi = L_1 = R = 1$ and $\kappa = 2\nu_1$, so that $\Sigma^* = \frac{1}{2}$, $\nu = \nu_1$, $x_0 = b$, $X = b + S_T$ and $\rho = 2\beta$. The complete rational values of β and S_T , the six test points and the cut points for Lemma 4.4 are in the data file `certificates.json` of the package. For instance, the point with the shortest chain, $N = 651$, has $b = \frac{1}{5000}$, $\nu_1 = \frac{102451}{12108600000}$,

$$\beta = \frac{899\,032\,669\,057\,340\,117\,937\,713\,848\,273\,401}{2 \cdot 10^{38}}, \quad S_T = \frac{500\,531\,032\,276\,116\,980\,167\,182\,393\,677\,011}{5 \cdot 10^{32}}.$$

N	b	ν_1	β (rounded)	S_T (rounded)	window of X	found by
651	1/5000	102451/12108600000	$4.4951633 \cdot 10^{-6}$	1.001062064552	$1.0 \cdot 10^{-13}$	run B
652	1/2000	17923/2125520000	$4.4810087 \cdot 10^{-6}$	1.000759357680	$1.4 \cdot 10^{-12}$	run B
652	1/100000	843117449/10 ¹⁴	$4.4781261 \cdot 10^{-6}$	1.001249059066	$3.5 \cdot 10^{-12}$	run A
653	1/100000	84019273/10 ¹³	$4.4622959 \cdot 10^{-6}$	1.001246181902	$1.2 \cdot 10^{-11}$	run A
655	1/1000	35807/4290250000	$4.4366601 \cdot 10^{-6}$	1.000251064899	$3.5 \cdot 10^{-11}$	run B
655	1/1000	8346141/10 ¹²	$4.4366641 \cdot 10^{-6}$	1.000251066023	$3.5 \cdot 10^{-11}$	run A
660	1/1000	7147/871200000	$4.3594821 \cdot 10^{-6}$	1.000236969109	$2.5 \cdot 10^{-10}$	run B
660	1/1000	6409/781250000	$4.3594225 \cdot 10^{-6}$	1.000236952092	$2.7 \cdot 10^{-10}$	run A
680	1/1000	7667/10 ⁹	$4.0691500 \cdot 10^{-6}$	1.000183091843	$4.6 \cdot 10^{-9}$	run A
690	1/1000	3709/(5 · 10 ⁸)	$3.9346029 \cdot 10^{-6}$	1.000157679206	$9.3 \cdot 10^{-9}$	run A
700	1/100	141/19600000	$3.8494839 \cdot 10^{-6}$	0.991137518398	$7.4 \cdot 10^{-9}$	run B
700	1/1000	359/(5 · 10 ⁷)	$3.8060948 \cdot 10^{-6}$	1.000133090436	$1.5 \cdot 10^{-8}$	run A
2000	1/100	7/10 ⁷	$3.63553 \cdot 10^{-7}$	0.99024985	$2.6 \cdot 10^{-6}$	first results
4000	1/100	811/(5 · 10 ⁹)	$8.3423707 \cdot 10^{-8}$	0.990099841186	$4.0 \cdot 10^{-6}$	run A

Table 2: The fourteen parameter points of Theorem 1.3; in all of them $\alpha = \gamma = \phi = L_1 = R = 1$ and $\kappa = 2\nu_1$. The values of β and S_T are rounded (exact for $N = 2000$: $\beta = 363553/10^{12}$, $S_T = 99024985/10^8$); the exact values are in the data file of the package. “Window of X ” (numerical): the relative length of the interval of $X = b + S_T$ in which the five roots persist, the other parameters being fixed; for (5) it is $6.6 \cdot 10^{-7}$. Runs A and B are the two independent verification runs.

Proof of Theorem 1.3. For each point the program of this note carries out the three steps of the proof of Theorem 1.2: positivity of the parameters and $q(\frac{1}{2}) = 0$; the sign pattern $+, -, +, -, +, -$ of P at six rational points increasing from x_0 to X ; and the exact count, five simple roots with P' of signs $-, +, -, +, -, -$, by Lemma 4.1. The count by Lemma 4.4, on the cut points of the data file, gives five for every point as well. The independent program of the third verification run, which reads only the parameters and the six test points and finds its own subdivisions, gives the same result by both methods for all fifteen points (Section 10). The theorem follows from Lemmas 3.2 and 3.4. $\square$

The eight points of run A and the five points of run B were found independently: each of the two verification runs searched with its own programs, in floating-point arithmetic, and then certified its points in exact arithmetic, and neither had the results of the other. Run B certified the exact count for its five points. Run A certified at least five steady states and the simplicity of five roots for its eight points; for these the exact count was added when this note was written, by the program of this note and by the counting program of run B, and it was confirmed by the program of the third run. The windows shrink rapidly as N decreases towards 651, and they stay thin for large N : at most about $4 \cdot 10^{-6}$ in the scans of run A up to $N = 50\,000$.

6 Upper bounds and small chains

Proof of Theorem 1.4. (a) By Lemma 3.2 and (13) the positive steady states correspond to the roots in $(0, S_T)$ of the polynomial

$$p(S) := \alpha \Sigma^* u(S) (S_T - S) - \beta S v(S), \quad u(S) := c_1 \left(\frac{b + \gamma S}{\phi} \right), \quad v(S) := t_0 \left(\frac{b + \gamma S}{\phi} \right),$$

with the same multiplicities as for P , since $p(S) = \frac{\phi \alpha \Sigma^*}{\gamma} P(x)$ and x is an increasing affine function of S . By Lemma 3.1(a) and because $b \geq 0$ and $\gamma, \phi > 0$, the polynomials $u(S) = \sum_{k=0}^{N-1} u_k S^k$ and $v(S) = \sum_{k=0}^N v_k S^k$ have positive coefficients. Write $p(S) = \sum_{k=0}^{N+1} a_k S^k$. Then

$$a_0 = \alpha \Sigma^* S_T u_0 > 0, \quad a_N = -\alpha \Sigma^* u_{N-1} - \beta v_{N-1} < 0, \quad a_{N+1} = -\beta v_N < 0,$$

while $a_k = \alpha \Sigma^* (S_T u_k - u_{k-1}) - \beta v_{k-1}$ for $1 \leq k \leq N-1$ can have either sign. The sequence $a_0, \dots, a_N$ has $N+1$ terms, begins with a positive and ends with a negative one; so its number of sign changes is odd and at most N , and a_{N+1} adds none. Thus the number V of sign changes of the coefficients of p is odd, $V \leq N$, and therefore $V \leq N-1$ if N is even. By Lemma 4.3, applied to p , which has $a_0 \neq 0 \neq a_{N+1}$, the polynomial p has at most V positive roots, counted with multiplicity. The parity statement is in Lemma 3.2.

(b) For $N \leq 2$ we get $V = 1$, and the number of positive steady states is odd; so it is one. For $N = 3$ and $N = 4$ we get $V \leq 3$.

(c) For the given parameters $q(s) = 2 \cdot 10^{-4}(1-s)^2 - 10^{-4}s$, so $\Sigma^* = \frac{1}{2}$, and $\nu = 10^{-4}$, $x_0 = 10^{-3}$, $X = 2$, $\rho = 10^{-2}$. From (6) with $N = 4$,

$$\begin{aligned} c_1 &= x^3 + 3\nu x^2 + (2\nu + 3\nu^2)x + \nu + 2\nu^2 + \nu^3, \\ t_0 &= x^4 + (1 + 4\nu)x^3 + (1 + 6\nu + 6\nu^2)x^2 + (1 + 6\nu + 9\nu^2 + 4\nu^3)x + 1 + 4\nu + 6\nu^2 + 4\nu^3 + \nu^4, \end{aligned}$$

and (8) gives the exact values

$$P\left(\frac{1}{20}\right) = -\frac{56\,246\,376\,730\,558\,049}{10^{21}} < 0, \quad P(1) = \frac{950\,630\,067\,903\,020\,079\,001}{10^{21}} > 0,$$

while $P(x_0) > 0 > P(X)$ by Lemma 3.2. So P has at least three roots in (x_0, X) , and by (b) exactly three; they are near $x = 0.0239, 0.0589$ and 1.9258 . $\square$

Remark 6.1. (1) The bound stated in [RS17, Section 3] is N for odd N and $N+1$ for even N ; it follows from the opposite signs of a_0 and a_{N+1} . The additional observation here is that a_N has the sign of a_{N+1} ; for $N = 3$ this is used in [RS17].

(2) For $N \geq 5$ the rule applied to p cannot give the bound three: for $N = 5$, $b = 0$, $\gamma = \phi = 1$, $\nu = \frac{1189}{10000}$, $\rho = \frac{9033}{10000}$, $X = \frac{132889}{25000}$ the coefficients of p have five sign changes, while P has one root in (x_0, X) (exact counts).

7 Stability

Proof of Theorem 1.5(a) and (b). (a) The formula for the sign of $\det J$ is Lemma 3.4(b). Let $P'(x) > 0$, so that $\det J \neq 0$ has the sign $(-1)^{N+1}$. J is a real matrix of size $N+2$. Its non-real eigenvalues come in conjugate pairs with positive products. Hence the number of real eigenvalues, with multiplicity, is congruent to N modulo 2, their product has the sign $(-1)^{N+1}$, and none is zero. So the number of negative real eigenvalues is congruent to $N+1$, and the number of positive real eigenvalues is odd. A

steady state at which the Jacobian has a positive eigenvalue is unstable. (By Lemma 3.4(c) there is also an eigenvalue with negative real part.)

(b) The signs of P' at the five roots are part of the exact counts in the proofs of Theorems 1.2 and 1.3. $\square$

If $P'(x) < 0$, the same count shows only that the number of positive real eigenvalues is even, and we know no argument that would give the stability of these steady states without computation.

7.1 The spectrum for $N = 1000$: part (c)

Let $n := N + 2 = 1002$ and $\chi(\lambda) := \det(J - \lambda)$, a polynomial of degree n . If $p_0 > p_1 > \dots > p_n$ are real numbers and the signs of $\chi(p_0), \chi(p_1), \dots, \chi(p_n)$ alternate, then χ has a zero in each of the n intervals (p_k, p_{k-1}) . These are then all zeros of χ : the eigenvalues of J are real and simple, and exactly one lies in each interval. With $p_0 = 0$ all eigenvalues are negative; with $p_0 = 1$ and $p_1 = 0$ exactly one is positive.

The certificate for a steady state consists of such a list of rational numbers: $p_0 = 0$ for the first, third and fifth steady state, $p_0 = 1$ and $p_1 = 0$ for the second and fourth; then the midpoints between consecutive approximate eigenvalues, which were computed in floating-point arithmetic and whose accuracy does not matter; and finally -5 . The signs of $\chi(p_k)$ are decided as follows.

- *Enclosure of the steady state.* S is enclosed in a rational interval of length less than 10^{-62} at whose end points f has certified opposite signs, inside one of the intervals (17). By (9) and Lemma 3.1(c), C_j lies between $\Sigma^* c_j(x^-)/t_0(x^+)$ and $\Sigma^* c_j(x^+)/t_0(x^-)$, where $x^- < x^+$ are the end points in the variable x ; these bounds are computed with directed rounding (Remark 4.2). Moreover $\Sigma = \frac{1}{2}$ exactly, so κ' is known exactly.
- *Evaluation of $\chi(p)$.* With the unknowns in the order $(C_N, \dots, C_1; C_0, S)$, the matrix $J - p$ has a tridiagonal leading block of size N , bordered by two rows and two columns. Gaussian elimination without pivoting on this block gives $\det(J - p)$ as the product of the N pivots and of the determinant of a 2×2 Schur complement. All operations are carried out in interval arithmetic with outward rounding, on the enclosures of S and of the C_j ; a sign is accepted only if every pivot interval and the interval of the 2×2 determinant exclude zero.

For each of the five steady states all 1003 signs are decided, and they alternate. This proves Theorem 1.5(c). The computation was made by run B with a program that uses the interval arithmetic of the library `mpmath` with 70 digits; it was run again for this note, with identical output.

A second program, written for this note, repeats the check with interval arithmetic on integers (448 fractional bits, every operation rounded outwards) and with a different evaluation of $\chi(p)$. By the proof of Lemma 3.4, $J_{CS} = \gamma d$ with $d = (C_1, C_2 - C_1, \dots, C_N - C_{N-1}, -C_N)^\top$ and $\mathbf{1}^\top d = 0$, and $J_{SC} = \alpha(S_T - S)e_1^\top$. If p is not an eigenvalue of A and $w := (A - p)^{-1}d$, then $\mathbf{1}^\top w = 0$, because $\mathbf{1}^\top(A - p) = -(\nu_1 + p)\mathbf{1}^\top$; hence $(J_{CC} - p)w = d$, and for $p \neq -(\nu_1 + \kappa')$ the Schur complement of $J_{CC} - p$ in $J - p$ gives

$$\chi(p) = \det(A - p) \cdot \frac{p + \nu_1 + \kappa'}{p + \nu_1} \cdot m(p), \quad m(p) = -\alpha C_1 - \beta - p - \alpha\gamma(S_T - S)w_1.$$

The program eliminates the tridiagonal matrix $A - p$ from the top, obtains $\det(A - p)$ as the product of the $N + 1$ pivots and w_1 by back substitution, and accepts a sign only if all pivot intervals and the interval of $m(p)$ exclude zero. Its test points are produced by a separate program and stored in a data file. It also decides all 1003 signs at each of the five steady states, and they alternate.

A third program, written by the third verification run, uses the ball arithmetic of the library Arb (700 bits) and neither of the two evaluations above. It encloses each root of P between two rational numbers at which P has exact opposite signs, computes the C_j from (9) in ball arithmetic, and evaluates $\chi(p)$ by the determinant formula for a rank-three perturbation of the block diagonal matrix with the blocks $J_{SS} - p$ and $A - p$, without the identities $\mathbf{1}^\top A = -\nu_1 \mathbf{1}^\top$ and $\mathbf{1}^\top d = 0$; its test points are computed by the program itself. Again all 1003 signs are decided at each steady state, and they alternate. At three test points per steady state it also computes $\det(J - p)$ by the general routine of the library, with the same result.

8 The smallest chain length: numerical evidence

Nothing in this section is proved, except the elementary fact marked as such.

8.1 A necessary condition

Let $G := t_0/c_1$ and $H(x) := (x - x_0)G(x)$. Since $P(x) = \rho c_1(x)[(X - x)/\rho - H(x)]$ and $c_1 > 0$, the positive steady states are the intersections of the graph of H with the straight line $x \mapsto (X - x)/\rho$; every line with negative slope meeting the graph of H over (x_0, ∞) arises from admissible ρ and X .

Proved: if the graph of H meets a straight line in k points of an interval, counted with multiplicity, then H'' has at least $k - 2$ zeros in that interval, counted with multiplicity, by Rolle's theorem. So if H'' has at most two zeros in (x_0, ∞) , counted with multiplicity, there are at most three positive steady states for all ρ and X , because their number with multiplicity is odd. (Run B constructed its examples with a converse: three suitable zeros of H'' give a line with five intersections. Since the examples are certified exactly, it is not needed.)

Where $G'' \neq 0$ we have $H'' = 2G' + (x - x_0)G'' = G'' \cdot (\eta(x) - x_0)$ with

$$\eta(x) := x + \frac{2G'(x)}{G''(x)}.$$

The function η depends only on N and ν , and the zeros of H'' are the solutions of $\eta(x) = x_0$. Numerically, in all cases examined, $G'' > 0 > G'$ in the range considered, and η has at most one *fold*, a local maximum followed by a local minimum. Three zeros of H'' then exist exactly when x_0 lies between the two extremal values of the fold. The fold exists for $\lambda := N^2\nu$ in a range that ends at a value $\lambda_c(N)$, where it closes in a cusp: as $\lambda \rightarrow \lambda_c(N)$ both extremal values tend to a number $\eta_c(N)$, which is the supremum of the levels x_0 admitting three zeros. Because $x_0 = b/\phi \geq 0$, on this description five positive steady states are possible exactly if $\eta_c(N) > 0$, and only for $b/\phi < \eta_c(N)$.

N	5	10	17	20	50	100	200	400	600
$\eta_c(N)$	-3.99	-11.10	-13.02	-12.84	-8.32	-4.58	-2.05	-0.598	-0.0815
$\lambda_c(N)$	6.997	4.342	3.913	3.846	3.665	3.620	3.599	3.590	3.587
N	640	649	650	651	652	660	700	1000	2000
$\eta_c(N)$	-0.0159	-0.0022	-0.00069	+0.00080	+0.0023	+0.0140	+0.0689	+0.343	+0.669
$\lambda_c(N)$	3.5865	3.5864	3.5864	3.5864	3.5864	3.5863	3.5860	3.5844	3.5826

Table 3: The cusp level $\eta_c(N)$ and the cusp parameter $\lambda_c(N) = N^2\nu$, computed by run B in floating-point arithmetic (recomputed for this note for the values of N shown). Numerical; not certified.

8.2 What was computed

The cusp level. Run B computed $\eta_c(N)$ for every integer N from 5 to 660, by bisection in λ on the sign of $\min \eta'$, in floating-point arithmetic, with the derivatives of G obtained by differentiating the recursion (6). The result is negative for each of the 646 values $N = 5, \dots, 650$, with minimum -13.02 at $N = 17$ and largest value -0.00069 at $N = 650$, and positive for $N = 651, \dots, 660$ (Table 3). A check with 40 digits gave, for $\lambda = \lambda_c - 10^{-5}$, the fold maximum -0.000704 for $N = 650$ and $+0.000790$ for $N = 651$; the third verification run obtained the same two values with a program of its own. The certified points agree with this picture: each of the fourteen points with $N \leq 2000$ has $b < \eta_c(N)$, for instance $b = \frac{1}{5000}$ for $N = 651$, and $N^2\nu$ lies between 3.518 and 3.586 for the twelve points with $N \leq 700$.

Grid scans of the necessary condition. Run B counted the sign changes of H'' for 254 values of N (all N from 5 to 120 and from 641 to 665, and a selection of other values up to 1000), for 1017 values of ν (from 10^{-13} to 10^3 , with a finer grid for $N^2\nu$ between 1.5 and 9), on 8000 points x up to 10^6 and for 62 levels x_0 from 0 to 10^5 , with additional levels inside every fold found. For every tested $N \leq 650$ the count never exceeded one. The scans with which the result was first obtained cover $N = 5, \dots, 40$ with four values of x_0 and twenty larger N up to 800 with $x_0 = 0$, on grids that reach only $x \approx 5$; they found the pattern for $N = 1000$ only.

Direct searches for five roots. Run A searched for a line with five intersections, in floating-point arithmetic, for all N from 5 to 100 with ten values of x_0 between 0 and 0.9 and 1301 values of ν , and for 27 values of N from 110 to 1000 with four values of x_0 . It found none for $N \leq 650$; on fine grids in $N^2\nu$ near the cusp it found windows for $N = 651$ (relative width $2 \cdot 10^{-13}$, at the limit of the arithmetic) and for every tested N from 652 to 50 000. Run B intersected the graph of H with about 300 000 random secant lines for sixteen values of N from 5 to 650, and the first search tested several thousand random admissible lines for each of twelve values of N from 5 to 40; neither found more than three intersections.

8.3 What the searches do not cover

All these computations use floating-point arithmetic on finite grids in ν , x and x_0 . A window can be much thinner than a grid: the scan of run B with step 0.02 in $N^2\nu$ reports at most one sign change of H'' for $N = 651, \dots, 654$, although certified examples with $N = 651, 652, 653$ exist (the relevant range of $N^2\nu$ has width below 0.001); and the random searches have no power against thin windows. The description of η (at most one fold, closing in a cusp) is an observation, not a theorem, and the margin at the upper end is small: $\eta_c(650) = -0.0007$. So the statement that there are at most three positive steady states for $5 \leq N \leq 650$ is supported by numerical evidence of three kinds; it is not proved, and we do not claim it.

9 A heuristic remark on the mechanism

This section explains, without proof and without any claim, why the phenomenon needs a long chain. The recursion (6) can be solved in closed form, and in the window $x = 1 - \xi/N$, $\nu = \lambda/N^2$ one finds, as $N \rightarrow \infty$,

$$\frac{N c_1(x)}{t_0(x)} \longrightarrow \Gamma(\xi; \lambda) := \frac{1}{2} [\omega \coth(\omega/2) - \xi] = \frac{1}{2}(\omega - \xi) + \frac{\omega}{e^\omega - 1}, \quad \omega := \sqrt{\xi^2 + 4\lambda}.$$

The steady states are the solutions of $c_1(x)/t_0(x) = \rho(x - x_0)/(X - x)$, that is, approximately, of $\Gamma(\xi; \lambda) = \hat{\rho}(\xi_0 - \xi)/(\xi - \xi_X)$ with $\hat{\rho} := N\rho$, $\xi_0 := N(1 - x_0)$ and $\xi_X := N(1 - X)$. The left-hand side does not depend on N . Its first term alone is what an infinite chain gives, for which the equation

reduces to a quartic and has at most three solutions; the additional solutions come from the term $\omega/(e^\omega - 1)$, which matters only for ξ of order ten, that is, for x within about $10/N$ of 1. The right-hand side is a hyperbola with the zero ξ_0 , and $\xi_0 \leq N$ because $b \geq 0$. Numerically, five solutions require a hyperbola that is nearly straight where the correction acts, hence a distant zero: ξ_0 must exceed about 650. The chain length thus enters only through the constraint $\xi_0 \leq N$. This picture is approximate: by the computations of run B the threshold value of $N(1 - \eta_c(N))$ is 650.5 for $N = 651$, 656.9 for $N = 1000$ and 663.0 for $N = 2000$.

10 Computations and reproducibility

Status of the statements. The lemmas of Sections 3 and 4, Theorem 1.4(a),(b) and Theorem 1.5(a) are proved without computation; Theorem 1.4(c) uses two rational numbers printed in its proof. Theorems 1.2 and 1.3 and Theorem 1.5(b) are computer-assisted with exact integer and rational arithmetic, including integer arithmetic with directed rounding (Remark 4.2); no floating-point number enters. Theorem 1.5(c) is computer-assisted with interval arithmetic. Section 8, Remark 5.1 and the column “window of X ” of Table 2 are numerical (floating-point or multiprecision arithmetic, not certified).

The package that accompanies this note has five parts (Table 4): the programs of the first results (`original/`), of the verification runs A and B, of this note (`writing_stage/`) and of the third verification run (`independent_run_2/`, the second stage of the verification). The folder `writing_stage/` contains the program of this note. Its data file `certificates.json` holds, as exact rational numbers, the fifteen parameter points, for each of them the six test points and the cut points for Lemma 4.4, and two controls with $N = 3$ and $N = 4$. The program `check_certificates.py` (Python, standard library only) reads this file and performs four checks for every point. *A*: for the six values of S it builds $C(S)$ by the three-term recursion read off (3), (4), scaled to $\Sigma = \Sigma^*$, verifies that the right-hand sides of (2)–(4) vanish exactly and that all C_j are positive, and computes the sign of the right-hand side of (1), without using P . *B*: the six signs of P by (16). *C*: the exact count by Lemma 4.1 (256 fractional bits, directed rounding). *D*: the exact count by Lemma 4.4 on the intervals between the cut points of the data file. The cut points were found by a separate search program, which the checker does not use; for $N = 1000$ and $N = 2000$ they are those of run A. The recorded output shows that all checks pass for all fifteen points and both controls. The program `rejection_tests.py` feeds the checker 22 corrupted versions of the data (changed parameters, chain lengths, test points, cut points and expected values) and records that each is rejected. All recorded runs were made on 11 October 2026 with Python 3.13.5; the computer-assisted statements presuppose that its integer arithmetic is correct and, for the first program for Theorem 1.5(c), that the interval arithmetic of `mpmath` 1.3.0 is. The programs of the third run (see the Verification paragraph) are a further check; some of them use `python-flint` 0.9.0 (the libraries FLINT and Arb).

Verification. In the first results Theorem 1.2 asserted at least five steady states, the exact count and the stability were numerical, and the smallest chain length was located only between 640 and 680. Three independent verification runs, all AI-assisted, followed; each wrote its own programs.

Runs A and B examined the first results, and neither saw the other. Run A compared the equations with both versions of [RS17] symbol by symbol; re-derived Lemma 3.2, in the form by fluxes given above, and checked it by a symbolic linear solve for $N \leq 7$; compared the polynomials printed in the source with ours (Remark 3.3); re-derived Theorem 1.4 and Lemma 3.4 line by line; recomputed the six signs by (16) and, without the polynomial, on the original equations; and added Certificate I, the exact signs of P' , and the eight points marked “run A” in Table 2. Run B derived the elimination independently; verified the original equations exactly at six values of S of its own choice; added Certificate II, the certificate for Theorem 1.5(c), the five points marked “run B”, and the criterion

statement	program	input	recorded output	
six signs, $N = 1000$, 2000	original/:	in the program	certify_five_steady_	E
the same; (2)–(4) at six S ; signs of P'	certify_five_steady_states.py		states.out	
Certificate I,	run A: a2_theoremA_exact.py	in the program	a2_theoremA_exact.out	E
$N = 1000, 2000$	run A: a5_exactly_five_vca.py	in the program	a5_exactly_five_vca_	E
the points of run A	run A: a7_other_examples.py	RUN_LOG.txt	a7_N*.out	F, E
(2)–(4) at six S , seven points	run B: b2_exact_ivt.py	in the program;	b2_exact_ivt_N*.out	E
Certificate II, seven points	run B: b4_exact_count.py	example_N*.json		
Theorem 1.5(c)		the same	b4_exact_count_N*.out	R
	run B: b6b_rigorous_spectrum.py	states_N1000.json	b6b_spectrum_	I
all fifteen points,	check_certificates.py	certificates.json	state*.out	
checks A–D			check_certificates_	E, R
rejection tests	rejection_tests.py	the same	output.txt	
			rejection_tests_	E, R
			output.txt	
Certificate II for the points of run A	cross_checks/: program of run B	pointA_N*.json	b4_on_pointA_N*.out	R
Theorem 1.5(c), second program	check_spectrum.py	spectrum_points_	check_spectrum_	I
all fifteen points, independent checker	independent_run_2/: r2_check.py	N1000.json	output.txt	
		parameters and test	r2_check_*.txt	E, R
		points of		
		certificates.json		
Theorem 1.5(c), third program	r2_spectrum.py	the same	r2_spectrum.txt	I
Section 8	run B: b8_cusp.py, b5_scan_smallN.py, b9_random_lines.py; run A: a6_scan.py; original/: scans	in the programs	listed in README.md	F

Table 4: The computations, with programs, inputs and recorded outputs (complete list: `README.md` of the package); lines 8 to 11 refer to the folder `writing_stage/`, lines 12 and 13 to `independent_run_2/`. Last column, the arithmetic: E exact integers or rationals; R integers with directed rounding; I interval or ball arithmetic; F floating point (numerical; in line 4 only the search).

and the computations of Section 8; ran all programs of the first results again, with identical outputs; and searched the literature. Both runs confirmed the theorems, and neither found an error in a proof. Their corrections concern the description of the sources and of the scans and the wording of the result; all were made (the corrections required by the three runs are listed in the verification report of the package).

When this note was written, the certificate programs of the first results and of both runs were run again from copies, with outputs identical to the recorded ones up to running times; the programs `check_certificates.py` and `check_spectrum.py` were written and run; and the counting program of run B was applied to the eight points of run A.

The third run examined the final text of this note and the programs written with it. It obtained the two Oberwolfach abstracts, both versions of [RS17] and the passage of [BR25] again from the sources, and the main text of [FVS⁺13] for the first time, and compared every sentence about them with the texts; re-derived the lemmas and proofs of Sections 3, 4, 6 and 7 line by line; and read the programs `check_certificates.py` and `check_spectrum.py` and the interval program of run B line by line, with the result that a run without failure proves the statements for which the note uses them, independently of the programs that searched for the parameter points. It then wrote programs of its

own from the statements of the note. Its checker reads only the parameters and the six test points; it computes Σ^* , inserts the states (9) into (2)–(4) as printed, and counts the roots by Lemma 4.1 and by Lemma 4.4, the latter on subdivisions that it finds itself and with two implementations (the polynomial arithmetic of the library FLINT, and plain integers). For each of the fifteen points it found exactly five roots, all simple, with P' of signs $-, +, -, +, -, +$, and $\gcd(P, P') = 1$. The run also eliminated the unknowns of (1)–(4) for $N \leq 3$ by Gröbner bases, without the structure used in Lemma 3.2, and found the polynomial of that lemma as a factor of the eliminant; checked Theorem 1.4(a) on 400 random rational parameter points and the identities of Lemma 3.4 exactly on 18; verified the numbers in the proof of Theorem 1.4(c), in Remark 6.1(2) and in Remark 3.3; recomputed Tables 1 and 2, Figure 1 and the numbers of Remark 5.1; compared Table 3 with the recorded outputs; and certified Theorem 1.5(c) with the third program of Section 7. It repeated the quick part of the package and the complete run of `check_certificates.py` from the archive; all recorded outputs were reproduced. It did not repeat the scans of Section 8. It found no wrong statement and no gap in a proof, and required fourteen corrections of the text and the package, all made; none changes a theorem.

Scope and priority. The model is that of François, Voisinne, Siggia, Altan-Bonnet and Vergassola [FVS⁺13], in the form studied by Rendall and Sontag [RS17]; the question is Rendall’s [Ren18, p. 488], see also [Ren17, pp. 1775–1776]. Rendall and Sontag prove [RS17, Theorem 1; Theorem 3.1 in the journal version] that the agonist-only system has exactly one positive steady state for $N = 1, 2$ and at most three, and three for suitable parameters, for $N = 3$; for larger N their Section 3 states the bound N (N odd) or $N + 1$ (N even), and the journal version adds that simulations found no parameters with more than three steady states for any N . The scope of our answer, as in Section 1.3: the agonist-only system; the chain length N treated as a free parameter, as in the Oberwolfach abstracts; five steady states proved for explicit parameter points with $N = 651, 652, 653, 655, 660, 680, 690, 700, 1000, 2000$ and 4000; more than three impossible for $N \leq 4$; nothing proved for $5 \leq N \leq 650$, where numerical searches found no example; hence the biologically motivated values of N , about 20 or less, are not covered, the parameter windows are extremely thin, and no biological conclusion is drawn. The full model with antagonist and the parameter values of the biological literature are not considered.

Later literature. Bali and Rendall [BR25] summarise [RS17], in their section on the validation of previous findings, as showing three positive steady states for certain parameters and the impossibility of exceeding this number, and they report exactly three for biologically motivated parameter values; since Theorem 1 of [RS17] concerns $N \leq 3$, no theorem is contradicted by the examples with large N given here. The dissertation of Brechmann [Bre24] summarises [RS17] in its Section 2.3 and is devoted to other models; a search of its text found nothing on $N \geq 4$ for this model.

What was read. Of [RS17]: the arXiv version (v1, the only one) completely, and of the journal version Sections 1 to 3 and, in the rest, the passages on N , on bounds and on simulations. The abstracts [Ren18] and [Ren17] completely. Of [FVS⁺13], in which the model was introduced: the main text, in the open copy at PubMed Central; it describes the model in words, takes $N = 5$ and does not mention multiple steady states of the model. Its equations are in the supplement, which we did not read; we rely on [RS17] for the equations, and the question is posed for the system as written there. Of [BR25]: the section named above. Of [Bre24]: Section 2.3. We also did not read the supplement of [BR25], the paper [ABG05], or the papers of Lipniacki et al. [LHFH08] and Zheng et al. [ZBB⁺05], which [Ren18] cites for multiple steady states in simulations of related models.

Searches. On 10 and 11 October 2026 the lists of works citing [RS17] in OpenAlex (12 works) and Semantic Scholar (16) were examined by title and abstract, and queries were made to arXiv, zbMATH, Crossref and Europe PMC and in seven web searches; the third verification run repeated the two lists and the queries. No answer to Problem 1.1 was found, and no statement on the number of steady states of this model for $N \geq 4$ beyond those quoted above. A search that finds nothing is

not a proof of novelty, and no priority is claimed. The method, a reduction to one polynomial and the exact evaluation of signs, is elementary; the reduction is the one indicated in [RS17, Section 3], and the determinant argument of Theorem 1.5(a) is standard.

AI-assisted tools were used to search the problem corpus and the literature, to find the arguments, to write and run the verification programs, and to help prepare this manuscript. The author has reviewed the proofs, the computations and the sources and is responsible for all claims. The note has not been peer reviewed.

References

- [ABG05] Grégoire Altan-Bonnet and Ronald N. Germain. Modeling T cell antigen discrimination based on feedback control of digital ERK responses. *PLoS Biology*, 3(11):e356, 2005. doi:10.1371/journal.pbio.0030356.
- [BR25] Yogesh Bali and Alan D. Rendall. A comparative mathematical modeling study of phenotypic approaches to T cell activation. *Scientific Reports*, 15:44233, 2025. doi:10.1038/s41598-025-32255-9.
- [Bre24] Pia Brechmann. *Mathematical models for T cell activation through kinetic proofreading*. Dissertation, Johannes Gutenberg-Universität Mainz, 2024. doi:10.25358/openscience-10595.
- [FVS⁺13] Paul François, Guillaume Voisinne, Eric D. Siggia, Grégoire Altan-Bonnet, and Massimo Vergassola. Phenotypic model for early T-cell activation displaying sensitivity, specificity, and antagonism. *Proceedings of the National Academy of Sciences*, 110(10):E888–E897, 2013. doi:10.1073/pnas.1300752110.
- [LHFH08] Tomasz Lipniacki, Beata Hat, James R. Faeder, and William S. Hlavacek. Stochastic effects and bistability in T cell receptor signaling. *Journal of Theoretical Biology*, 254(1):110–122, 2008. doi:10.1016/j.jtbi.2008.05.001.
- [Ren17] Alan D. Rendall. Mathematical models for T-cell activation. *Oberwolfach Reports*, 14(2):1775–1776, 2017. Abstract (joint work with E. D. Sontag) in Report 28/2017, *Reaction Networks and Population Dynamics*. doi:10.4171/OWR/2017/28.
- [Ren18] Alan D. Rendall. Initiation of T cell signalling. *Oberwolfach Reports*, 15(1):487–489, 2018. Abstract (joint work with E. D. Sontag) in Report 8/2018, *The Mathematics of Mechanobiology and Cell Signaling*. doi:10.4171/OWR/2018/8.
- [RS17] Alan D. Rendall and Eduardo D. Sontag. Multiple steady states and the form of response functions to antigen in a model for the initiation of T-cell activation. *Royal Society Open Science*, 4(11):170821, 2017. arXiv:1705.00149, doi:10.1098/rsos.170821.
- [ula26] ulamai. UnsolvedMath. Hugging Face dataset, <https://huggingface.co/datasets/ulamai/UnsolvedMath>, 2026. Version 1.6.0; record OWR-15993-009.
- [ZBB⁺05] Yanan Zheng, Venkataramanan Balakrishnan, Greg Buzzard, Robert Geahlen, Marietta Harrison, and Ann Rundell. Modeling and analysis of early events in T-lymphocyte antigen-activated intracellular-signaling pathways. *Journal of Computational and Applied Mathematics*, 184(1):320–341, 2005. doi:10.1016/j.cam.2004.08.015.