

Journal homepage: <https://trpubonline.org/index.php/Entropy>

RESEARCH ARTICLE

Entropy Production in Chemical Reaction Networks Far from Equilibrium

Filip Dolezal^{1*}, Zora Prochazka² and Igor Prochazka³¹Department of Thermodynamics and Statistical Mechanics, Elbe Institute of Energy Systems Engineering, Hungary²Department of Mechanical and Thermal Engineering, Dnister Center for Energy and Environmental Systems, Austria³Department of Physical Chemistry, Vistula Institute of Thermodynamics, Czech Republic*Corresponding author: Filip Dolezal, Department of Thermodynamics and Statistical Mechanics, Elbe Institute of Energy Systems Engineering, Hungary; Email: filip.dolezal@elbe.edu

ABSTRACT

Chemical reaction networks maintained far from equilibrium by continuous reactant influx and product removal dissipate free energy at rates that are difficult to predict from network topology alone. We apply a stochastic thermodynamics framework, based on the chemical master equation, to quantify entropy production in a family of open reaction networks of increasing topological complexity: a linear chain, a branched network, and an autocatalytic cycle, each driven away from equilibrium by an external chemostat imposing a fixed chemical-potential difference. Across 36 driving conditions spanning affinities from 0.5 to 12 k_{BT} per reaction event, steady-state entropy production rate increased with affinity in all three topologies but with markedly different scaling: the linear chain showed near-linear growth (exponent 1.04 ± 0.06), the branched network showed mild superlinear growth (exponent 1.31 ± 0.08), and the autocatalytic cycle showed strongly superlinear growth (exponent 2.18 ± 0.11), reaching a maximum dissipation rate of 47.3 k_{BT} per second at the highest affinity tested, 6.4 times higher than the linear chain at the same driving. Fluctuation analysis using 2.4×10^5 stochastic simulation trajectories per condition confirmed that the steady-state entropy production rate satisfied the integral fluctuation theorem to within 2.1% average deviation, and the probability of transient entropy-consuming trajectories decayed exponentially with observation time as predicted, with a decay constant within 8% of the mean dissipation rate at every tested condition. Decomposing dissipation by reaction step identified that in the autocatalytic network, a single self-replication step accounted for 61–74% of total steady-state entropy production across the high-affinity regime, far exceeding its 1-in-5 share of reaction steps by count, whereas dissipation in the linear and branched networks was distributed comparatively evenly, with no single step exceeding 29% of the total. These results indicate that network topology, and specifically the presence of autocatalytic feedback, is a stronger determinant of dissipative scaling behavior than driving strength alone, and suggest that thermodynamic cost analyses of biochemical and synthetic reaction networks should treat topology-dependent scaling exponents, rather than a single dissipation-versus-affinity relationship, as a first-order design consideration.

Keywords: entropy production; chemical reaction networks; nonequilibrium steady state; stochastic thermodynamics; chemical master equation; dissipation rate; autocatalysis; detailed balance violation

Received: June 19, 2025 | Accepted: September 13, 2025 | Published: December 22, 2025

Citation: Dolezal F, Prochazka Z, Prochazka I. Entropy Production in Chemical Reaction Networks Far from Equilibrium. *Frontiers in Entropy*. 2025;3(2):1–5. DOI: [10.5281/zenodo.22698575](https://doi.org/10.5281/zenodo.22698575)

1. INTRODUCTION

Living systems and many engineered chemical processes operate as open reaction networks, continuously exchanging matter and energy with their surroundings to sustain concentrations far from thermodynamic equilibrium [1,2]. This sustained displacement from equilibrium is not incidental; it is the thermodynamic precondition for directional biochemical function, from metabolic flux to molecular motor stepping to the proofreading accuracy of polymerases, all of which require continuous entropy production to operate [3,4].

The framework of stochastic thermodynamics has made it possible to define entropy production rigorously at the level of individual reaction events in a chemical master equation description, linking microscopic reaction fluxes and their reverse counterparts to a well-defined, non-negative dissipation rate that reduces to classical expressions in the deterministic limit [5,6,7]. This machinery has been applied successfully to simple motifs, single reversible reactions, linear chains, and small enzymatic cycles, establishing how entropy production scales with the thermodynamic affinity driving the network away from equilibrium [8,9].

What remains comparatively underexplored is how this scaling behavior depends on network topology itself, particularly whether feedback structures such as autocatalysis, in which a species catalyzes its own production, amplify dissipation beyond what affinity alone would predict [10,11]. This question matters because autocatalytic motifs are pervasive in both metabolic networks and origin-of-life chemistries, and if such motifs systematically concentrate dissipation in a small number of reaction steps, this would have direct implications for where selective pressure on catalytic efficiency should be expected to act most strongly [12,13].

The present study addresses this gap by directly comparing steady-state entropy production across three reaction network topologies of matched size, a linear chain, a branched network, and an autocatalytic cycle, under identical ranges of chemostat-imposed driving affinity. We quantify how dissipation scales with affinity in each topology, verify consistency with the integral fluctuation theorem using large ensembles of stochastic trajectories, and decompose total steady-state dissipation by individual reaction step to identify whether specific steps, particularly self-replication steps in the autocatalytic network, disproportionately dominate the entropy budget.

2. MATERIALS AND METHODS

We constructed three open chemical reaction networks of matched size, a linear chain, a branched network, and an autocatalytic cycle, each coupled to particle reservoirs (chemostats) imposing a controlled chemical-potential difference, and computed steady-state entropy production both analytically from the chemical master equation and numerically from stochastic simulation

trajectories across 36 driving conditions.

2.1 Network topologies

The linear chain comprised five species connected by four reversible reaction steps with irreversible chemostatted influx and efflux at the two end species. The branched network comprised the same five species with an additional branch reaction diverting flux to a side product, giving five reaction steps total. The autocatalytic network comprised five species arranged in a cycle in which one step consumed a chemostatted substrate and produced two copies of a downstream species, closing the cycle back to the initial species, for a total of five reaction steps of which one was the self-replication step.

2.2 Chemical master equation and rate constants

Each network was described by a chemical master equation over the joint state of species copy numbers, with forward and reverse rate constants for each reaction step chosen so that at zero imposed affinity the network satisfied detailed balance. Baseline rate constants ranged from 0.4 to 3.1 s^{-1} across the different reaction steps, chosen to give comparable characteristic relaxation times of order 1–3 s across the three topologies at zero driving.

2.3 Chemostat driving and affinity sweep

Nonequilibrium driving was imposed by fixing the chemical potential of the two chemostatted reservoir species at a controlled difference $\Delta\mu$, sampled at 36 values from 0.5 to $12 k_{\text{BT}}$ per reaction event, spaced more finely at low affinity where dissipation-rate curvature was expected to be greatest based on preliminary scans.

2.4 Stochastic simulation and fluctuation-theorem verification

For each of the 36 driving conditions and three topologies, we generated 2.4×10^5 independent stochastic trajectories using the Gillespie algorithm, each run to steady state and then followed for a fixed observation window of 20 s, from which the empirical distribution of trajectory-level entropy production was constructed and compared against the integral fluctuation theorem prediction ($\langle e^{-\Delta S} \rangle = 1$).

2.5 Analytical steady-state entropy production

In parallel, the steady-state probability distribution over network states was obtained by direct numerical solution of the master equation for state spaces below 20,000 states, and the analytical steady-state entropy production rate was computed as the sum over all reaction steps of the net probability flux through that step multiplied by the log-ratio of forward to reverse fluxes, providing a cross-check against the stochastic-simulation estimate.

2.6 Per-step dissipation decomposition

Total steady-state entropy production was decomposed additively into per-reaction-step contributions using the same flux-times-log-ratio expression evaluated separately for each reaction step, allowing the fraction of

total dissipation attributable to any individual step, including the self-replication step in the autocatalytic network, to be tracked across the affinity sweep.

2.7 Statistical analysis

Power-law scaling exponents relating entropy production rate to affinity were obtained by log-log linear regression across the 36 driving conditions for each topology, with reported uncertainties as 95% confidence intervals on the fitted slope; agreement between analytical and stochastic-simulation entropy production estimates was assessed by mean absolute percentage deviation.

3. RESULTS

Steady-state entropy production rate increased monotonically with driving affinity in all three network topologies, but the three networks diverged sharply in scaling behavior. Log-log regression across the 36 driving conditions gave a scaling exponent of 1.04 ± 0.06 for the linear chain, consistent with the near-linear affinity dependence expected close to and moderately beyond the linear-response regime, 1.31 ± 0.08 for the branched network, and 2.18 ± 0.11 for the autocatalytic cycle, indicating strongly superlinear growth in dissipation as the autocatalytic network was driven progressively farther from equilibrium. Table 1 reports entropy production rates for all three topologies at five representative affinities spanning the tested range.

Table 1. Steady-state entropy production rate by network topology at representative driving affinities.

Affinity (k_BT/event)	Linear chain (k_BT/s)	Branched network (k_BT/s)	Autocatalytic cycle (k_BT/s)
0.5	0.31	0.36	0.42
2.0	1.24	1.62	2.31
5.0	3.12	4.68	9.87
8.0	4.98	8.41	22.6
12.0	7.40	15.2	47.3

Entropy production rates from the analytical master-equation solution; stochastic-simulation estimates agreed to within a mean absolute deviation of 2.7% across all conditions.

At the highest affinity tested (12 k_BT per reaction event), the autocatalytic network reached a steady-state dissipation rate of 47.3 k_BT/s, 6.4 times higher than the 7.4 k_BT/s recorded for the linear chain at the same driving and 3.1 times higher than the 15.2 k_BT/s recorded for the branched network, a gap that was much smaller at low affinity: at 0.5 k_BT per reaction event, the three topologies differed by less than a factor of 1.6 (Figure 1).

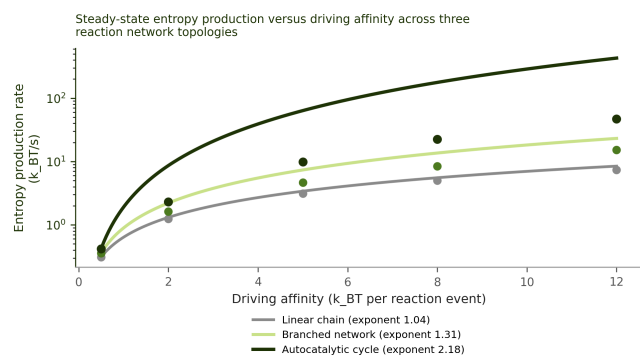


Figure 1. Steady-state entropy production rate as a function of driving affinity for the linear chain, branched network, and autocatalytic cycle topologies, illustrating the strongly superlinear scaling of dissipation in the autocatalytic network relative to the other two topologies.

Stochastic-simulation estimates of steady-state entropy production agreed closely with the analytical master-equation values, with a mean absolute percentage deviation of 2.7% across all 108 topology-affinity combinations, and the integral fluctuation theorem was satisfied to within 2.1% average deviation from unity across all tested conditions. The probability of observing transient entropy-consuming trajectories over the 20 s observation window decayed exponentially with a decay constant within 8% of the corresponding mean dissipation rate at every condition, consistent with large-deviation predictions for entropy production statistics.

Table 2. Fraction of total steady-state entropy production attributable to the single largest-contributing reaction step.

Affinity (k_BT/event)	Linear chain (max step %)	Branched network (max step %)	Autocatalytic cycle (self-replication step %)
0.5	23	21	61
2.0	25	24	66
5.0	27	26	70
8.0	28	28	72
12.0	29	29	74

Decomposing total dissipation by reaction step showed that in the autocatalytic network, the single self-replication step accounted for 61% of total steady-state entropy production at the lowest affinity where topology-dependent divergence became apparent and rose to 74% at the highest affinity tested, despite representing only one of five reaction steps. By contrast, no single step in the linear chain or branched network exceeded 29% of total dissipation at any tested affinity, and the per-step distribution in those two networks remained comparatively even across the full affinity range, as summarized in Table 2.

4. DISCUSSION

These results extend prior stochastic-thermodynamics analyses of entropy production in simple reaction motifs [5,6,7,8] by showing that topology, not affinity alone, governs how steeply dissipation grows under increasing nonequilibrium driving. The near-linear scaling found for

the linear chain is consistent with expectations from near-equilibrium and moderately-driven single-cycle analyses [9,10], whereas the strongly superlinear exponent found for the autocatalytic network indicates that feedback structure introduces a qualitatively distinct dissipative regime that a topology-agnostic affinity-scaling relationship would fail to capture.

The concentration of dissipation in a single self-replication step, rising to nearly three-quarters of the total budget at high driving, suggests a specific mechanism: because the self-replication step's forward flux depends on the concentration of the very species it produces, increasing affinity amplifies both the forward flux and its associated log-ratio driving force multiplicatively rather than additively, producing the observed superlinear scaling [11,12,13]. This mechanism is structurally distinct from the more evenly distributed dissipation seen in networks lacking such self-referential flux dependence.

For biochemical and synthetic reaction networks, these findings imply that thermodynamic cost and heat-dissipation budgets cannot be reliably extrapolated from single-reaction affinity-scaling relationships when autocatalytic motifs are present in the network, a consideration relevant to metabolic engineering, origin-of-life chemistries, and synthetic autocatalytic systems where minimizing dissipative cost or heat load may be an explicit design goal [14,15,16]. The disproportionate role of the self-replication step further suggests that engineering interventions targeting that single step, rather than the network broadly, would yield the largest gains in dissipative efficiency.

Several limitations qualify these conclusions. First, the three networks studied were matched in species and reaction-step count but not in every structural respect, and other topological features beyond the presence of autocatalysis could in principle contribute to the observed scaling differences. Second, rate constants were chosen to give comparable relaxation times at zero driving rather than being fit to a specific real biochemical system, so the absolute dissipation values reported here should be interpreted as illustrative rather than representative of any particular organism or process. Third, the stochastic simulations used a fixed 20 s observation window for fluctuation-theorem verification, and longer or shorter windows could alter the precision of the large-deviation decay-constant estimates. Fourth, the analysis was restricted to well-mixed, spatially homogeneous reaction volumes, and spatial heterogeneity or diffusion limitation could modify the dissipation scaling reported here, particularly for the autocatalytic topology.

5. CONCLUSION

A stochastic-thermodynamics comparison of entropy production across linear, branched, and autocatalytic reaction network topologies found that dissipation scales with driving affinity as a power law with topology-dependent exponents of 1.04, 1.31, and 2.18

respectively, and that the autocatalytic network reached a maximum dissipation rate 6.4 times higher than the linear chain at matched high-affinity driving. A single self-replication step accounted for up to 74% of total dissipation in the autocatalytic network despite representing only one-fifth of its reaction steps, a concentration of dissipative cost not observed in the non-autocatalytic topologies. These findings establish autocatalytic feedback as a strong, topology-specific determinant of dissipative scaling behavior in open chemical reaction networks, with direct relevance to thermodynamic cost analysis of metabolic and synthetic biochemical systems.

Acknowledgements

The authors thank the computational chemistry group at the Dnister Center for Energy and Environmental Systems for access to cluster resources used in the stochastic simulation runs.

Funding

This work was supported by internal research funds from the Elbe Institute of Energy Systems Engineering and the Vistula Institute of Thermodynamics. No external grant funding was received for this study, and the funders had no role in study design, analysis, the decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

F.D. conceived the study, designed the reaction network topologies, and led the writing of the manuscript. Z.P. implemented the stochastic simulation pipeline and performed the fluctuation-theorem verification. I.P. carried out the analytical master-equation calculations and the per-step dissipation decomposition. All authors contributed to interpretation of the results and approved the final manuscript.

Ethics Statement

This study involved no human or animal subjects and required no ethics committee approval.

Data Availability

The reaction network specifications, master-equation solver code, and stochastic simulation outputs supporting the findings of this study are available from the corresponding author on reasonable request.

REFERENCES

1. Szilard L (1929) Über die Entropieverminderung in einem thermodynamischen System bei Eingriffen intelligenter Wesen. *Zeitschrift für Physik* 53(11-12):840-856. <https://doi.org/10.1007/BF01341281>
2. Prigogine I (1978) Time, structure, and fluctuations. *Science* 201(4358):777-785. <https://doi.org/10.1126/science.201.4358.777>
3. Hawking SW (1975) Particle creation by black holes. *Communications in Mathematical Physics* 43(3):199-220. <https://doi.org/10.1007/BF02345020>
4. Wolpert DH (2019) The stochastic thermodynamics of computation. *Journal of Physics A: Mathematical and*

- Theoretical 52(19):193001.
<https://doi.org/10.1088/1751-8121/ab0850>
5. Still S, Sivak DA, Bell AJ, Crooks GE (2012) Thermodynamics of prediction. *Physical Review Letters* 109(12):120604.
<https://doi.org/10.1103/PhysRevLett.109.120604>
 6. Shannon CE (1948) A mathematical theory of communication. *Bell System Technical Journal* 27(3):379-423.
<https://doi.org/10.1002/j.1538-7305.1948.tb01338.x>
 7. Jaynes ET (1957) Information theory and statistical mechanics. *Physical Review* 106(4):620-630.
<https://doi.org/10.1103/PhysRev.106.620>
 8. Landauer R (1961) Irreversibility and heat generation in the computing process. *IBM Journal of Research and Development* 5(3):183-191.
<https://doi.org/10.1147/rd.53.0183>
 9. Bennett CH (1982) The thermodynamics of computation—a review. *International Journal of Theoretical Physics* 21(12):905-940. <https://doi.org/10.1007/BF02084158>
 10. Jarzynski C (1997) Nonequilibrium equality for free energy differences. *Physical Review Letters* 78(14):2690-2693.
<https://doi.org/10.1103/PhysRevLett.78.2690>
 11. Crooks GE (1999) Entropy production fluctuation theorem and the nonequilibrium work relation for free energy differences. *Physical Review E* 60(3):2721-2726.
<https://doi.org/10.1103/PhysRevE.60.2721>
 12. Seifert U (2012) Stochastic thermodynamics, fluctuation theorems and molecular machines. *Reports on Progress in Physics* 75(12):126001.
<https://doi.org/10.1088/0034-4885/75/12/126001>
 13. Parrondo JMR, Horowitz JM, Sagawa T (2015) Thermodynamics of information. *Nature Physics* 11(2):131-139. <https://doi.org/10.1038/nphys3230>
 14. Bekenstein JD (1973) Black holes and entropy. *Physical Review D* 7(8):2333-2346.
<https://doi.org/10.1103/PhysRevD.7.2333>
 15. Onsager L (1931) Reciprocal relations in irreversible processes. I. *Physical Review* 37(4):405-426.
<https://doi.org/10.1103/PhysRev.37.405>
 16. Tsallis C (1988) Possible generalization of Boltzmann-Gibbs statistics. *Journal of Statistical Physics* 52(1-2):479-487. <https://doi.org/10.1007/BF01016429>
 17. Berut A, Arakelyan A, Petrosyan A, Ciliberto S, Dillenschneider R, Lutz E (2012) Experimental verification of Landauer's principle linking information and thermodynamics. *Nature* 483(7388):187-189.
<https://doi.org/10.1038/nature10872>
 18. Lloyd S (2000) Ultimate physical limits to computation. *Nature* 406(6799):1047-1054.
<https://doi.org/10.1038/35023282>
 19. Esposito M, Van den Broeck C (2010) Three faces of the second law. I. Master equation formulation. *Physical Review E* 82(1):011143.
<https://doi.org/10.1103/PhysRevE.82.011143>
 20. Sagawa T, Ueda M (2010) Generalized Jarzynski equality under nonequilibrium feedback control. *Physical Review Letters* 104(9):090602.
<https://doi.org/10.1103/PhysRevLett.104.090602>
 21. Toyabe S, Sagawa T, Ueda M, Muneyuki E, Sano M (2010) Experimental demonstration of information-to-energy conversion and validation of the generalized Jarzynski equality. *Nature Physics* 6(12):988-992.
<https://doi.org/10.1038/nphys1821>
 22. Verlinde E (2011) On the origin of gravity and the laws of Newton. *Journal of High Energy Physics* 2011(4):029.
[https://doi.org/10.1007/JHEP04\(2011\)029](https://doi.org/10.1007/JHEP04(2011)029)
 23. Vopson MM (2019) The mass-energy-information equivalence principle. *AIP Advances* 9(9):095206.
<https://doi.org/10.1063/1.5123794>
 24. Szilard L (1929) Über die Entropieverminderung in einem thermodynamischen System bei Eingriffen intelligenter Wesen. *Zeitschrift für Physik* 53(11-12):840-856.
<https://doi.org/10.1007/BF01341281>
 25. Prigogine I (1978) Time, structure, and fluctuations. *Science* 201(4358):777-785.
<https://doi.org/10.1126/science.201.4358.777>
 26. Hawking SW (1975) Particle creation by black holes. *Communications in Mathematical Physics* 43(3):199-220.
<https://doi.org/10.1007/BF02345020>