BIOLOGICAL HOMOCHIRALITY

Noise-Induced Symmetry Breaking

Far from Equilibrium

Homochirality: one of the universal features of life

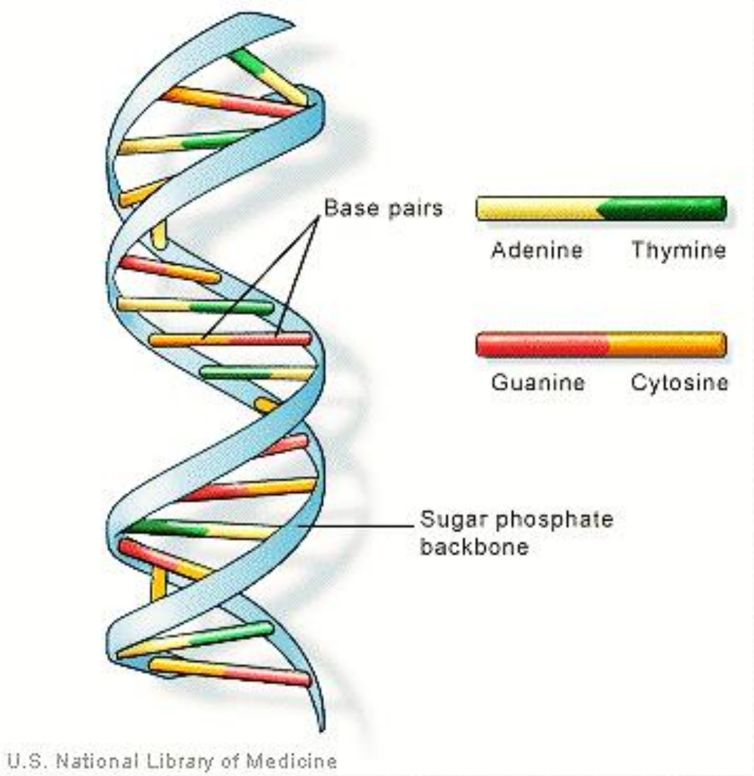
Together with **Canonical genetic code** , **homochirality** is one of the universal features of life on Earth.

- **Canonical genetic code:** refers to the set of rules by which the genetic information in DNA and RNA is translated into proteins.
- **Homochirality**: the single-handedness of all biological amino acids and sugars

The only universal process common to all life is, of course, **evolution,** and so it is natural to seek an explanation for biological homochirality in these terms.

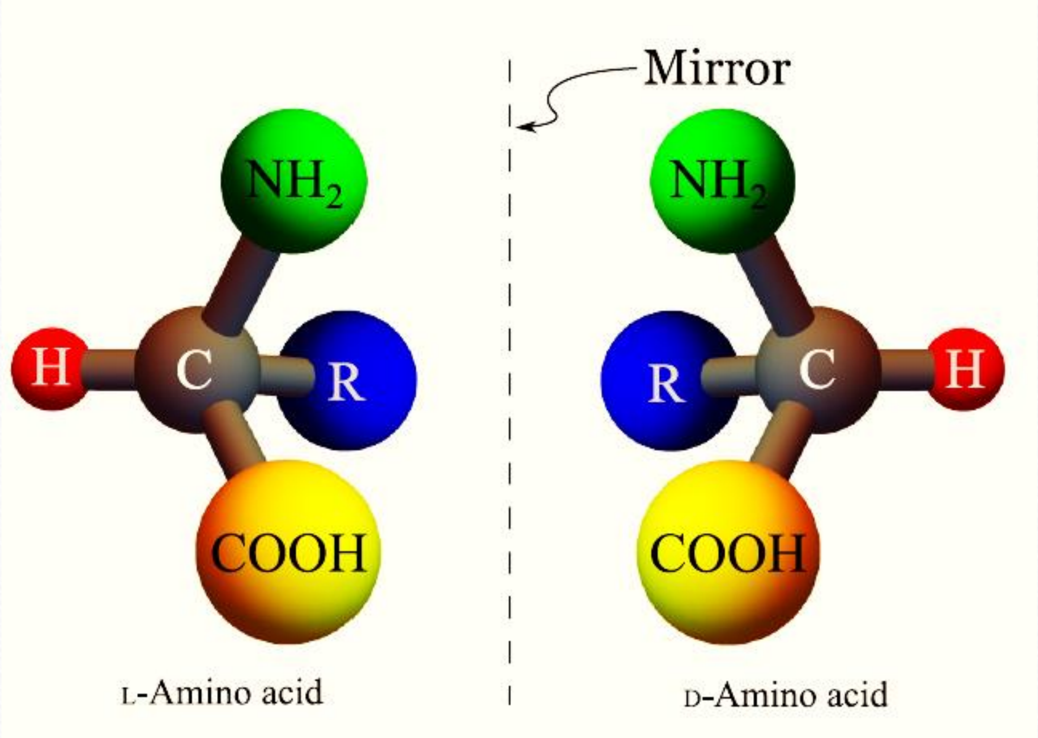
Homochirality: Where does it show itself?

The famous **double helix structure of DNA** is **a result of the chirality** of the sugar molecules in its backbone. Despite the diversity of proteins and their functions virtually all chiral biological amino acids are L-chiral, while all sugars are D-chiral.



Homochirality: What does it mean?

Molecules that are not superimposable on their mirror image are called **chiral** (Greek for hand), and the atom surrounded by four different groups is known as the **chiral center of the molecule**.



Some Homochirality Jargon

- **enantiomer:** each category of chiral molecules.
- **racemic solution**: solutions of 50% right-handed and 50% left-handed molecules.
- **homochiral solution:** solution of all left-handed or all right-handed molecules.

The Mystery of Homochirality

Early Earth

The initial state was symmetric: solution of achiral molecules

The
laws of physics are symmetric

We expect a symmetric final state: a biosphere made of a racemic solution of chiral molecules

Homochirality: A symmetry-breaking case

A phenomenon in which the **initial state** and the **corresponding laws of physics** are symmetric with respect to a particular transformation, but the final state of the system violates that symmetry, is called a symmetry breaking

Homochirality: Possible Explaining Theories

Theories for symmetry-breaking problems

Homochirality

- **Explicit Symmetry-Breaking**
  - Weak interactions
  - Polarized light interactions
- **Spontaneous Symmetry-Breaking**
  - Frank's Model

Homochirality: Explicit Symmetry-Breaking Theories

the laws of physics are only approximately symmetric, or there is an asymmetric perturbation to the system

- if life was formed from **chiral** organic molecules that were produced under a steady radiation of **circularly polarized** light, the **asymmetric interaction** of different enantiomers of chiral molecules with the light over hundreds of millions of years could lead to a significant enantiomeric excess
- Unlike electromagnetic interactions, the weak interaction violates mirror symmetry

A common weakness of explicit symmetry-breaking mechanisms is that the **homochirality achieved is only partial**

Homochirality: Spontaneous Symmetry-Breaking Theories

the governing laws are perfectly symmetric, and as a result, the symmetric state is a final solution, but it may be an **unstable solution**. In this case, even the slightest perturbation to the system moves the system away from the symmetric state.

Spontaneous Symmetry-Breaking Theories: Frank's Model

Auto-Catalysis Reaction

$$A + \mathrm{D} \xrightarrow{k_a} 2\mathrm{D}, \qquad A + \mathrm{L} \xrightarrow{k_a} 2\mathrm{L}.$$

Chiral Inhibition Reaction

$$\mathrm{D} + \mathrm{L} \xrightarrow{k_i} 2A.$$

Spontaneous Symmetry-Breaking Theories: Frank's Model

Auto-Catalysis Reaction

$$A + \mathrm{D} \xrightarrow{k_a} 2\mathrm{D}, \quad A + \mathrm{L} \xrightarrow{k_a} 2\mathrm{L}$$

self-replication

Chiral Inhibition Reaction

$$\mathrm{D} + \mathrm{L} \xrightarrow{k_i} 2A.$$

Law of Mass Action

$$\frac{d[A]}{dt} = 2k_i\,[\mathrm{D}]\,[\mathrm{L}] - k_a\,[A]\,([\mathrm{D}] + [\mathrm{L}])$$

$$\frac{d[\mathrm{D}]}{dt} = k_a\,[A]\,[\mathrm{D}] - k_i\,[\mathrm{L}]\,[\mathrm{D}],$$

$$\frac{d[\mathrm{L}]}{dt} = k_a\,[A]\,[\mathrm{L}] - k_i\,[\mathrm{D}]\,[\mathrm{L}].$$

Spontaneous Symmetry-Breaking Theories: Frank's Model

The State of the System

$$\omega = \frac{[\mathrm{D}] - [\mathrm{L}]}{[\mathrm{D}] + [\mathrm{L}]}$$

$$\frac{d\omega}{dt} = \frac{1}{2}k_i([\mathrm{D}] + [\mathrm{L}])\omega(1 - \omega^2)$$

Spontaneous Symmetry-Breaking Theories: Frank's Model

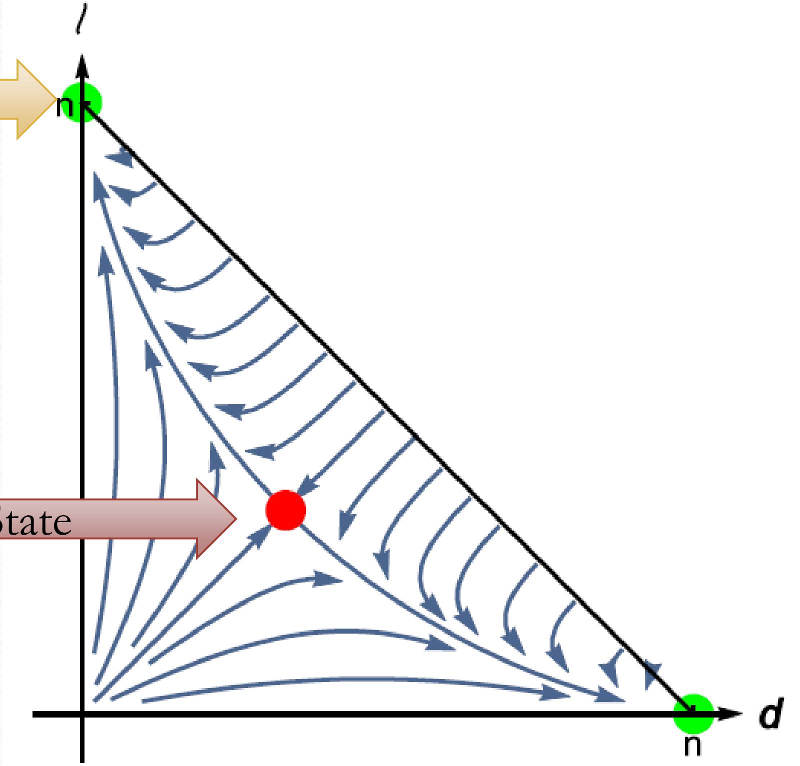
Homochiral State

The State of the System

$$\omega = \frac{[\mathrm{D}] - [\mathrm{L}]}{[\mathrm{D}] + [\mathrm{L}]}$$

Racemic State

$$\frac{d\omega}{dt} = \frac{1}{2}k_i([\mathrm{D}] + [\mathrm{L}])\omega(1 - \omega^2)$$



(a) $A + \mathrm{D} \to 2\mathrm{D}$, $A + \mathrm{L} \to 2\mathrm{L}$, $\mathrm{D} + \mathrm{L} \to 2A$

The Problems with Frank's Model

Although **autocatalysis** is an expected prerequisite for early life **self-replicators**, the mutually antagonistic relationship between the two chiral molecules **(~~chiral inhibition~~)** does not seem to be biologically necessary

New Proposed Model

Let's remove the **chiral inhibition** reaction and replace it by **nonautocatalyctic** and **decay reactions**

$$A + \mathrm{D} \xrightarrow{k_a} 2\mathrm{D}, \qquad A + \mathrm{L} \xrightarrow{k_a} 2\mathrm{L}$$

$$A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{D}, \qquad A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{L}.$$

This model can be interpreted as a model for the evolution of early life where primitive **chiral self-replicators** can be produced randomly through **nonautocatalytic** processes at very low rates; the **self-replication** is modeled by **autocatalysis** while the **decay reaction** is a model for the **death process**.

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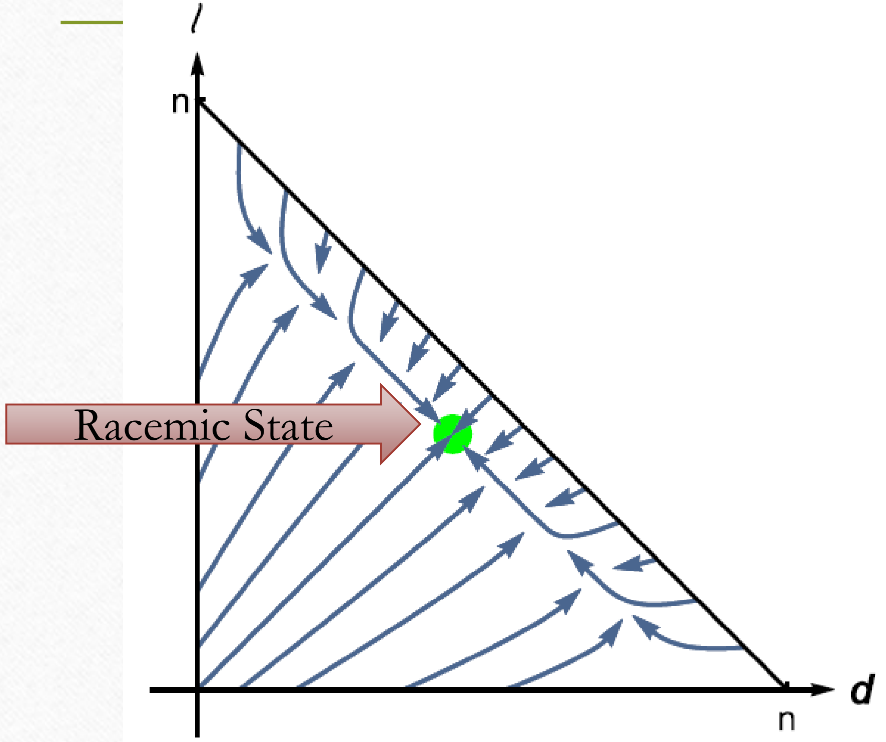
New Proposed Model: Deterministic Approach



(c) $A + \textsc{d} \rightarrow 2\textsc{d}$, $A + \textsc{l} \rightarrow 2\textsc{l}$,
$\textsc{d} \rightleftharpoons A$, $\textsc{l} \rightleftharpoons A$

Spoiler!

when the effect of chemical number fluctuations from self-replication is taken into account, the system can transition to homochirality when the autocatalysis is the dominant mechanism for the production of the chiral molecules

A Change of Approach: Revisiting our Assumptions

Law of mass action: the **expected value** of the number of collisions per unit time is proportional to the product of the concentrations of the reactants.

Near equilibrium, a system of a large number of interacting chemicals follows Boltzmann statistics and can be approximated by its **expected value**.

the **expected value** of number of collisions is used instead of the actual **probability distribution of the number of collisions per unit time**.

A Change of Approach: Far from Equilibrium Conditions

interpret the **law of mass action** as the **probability** per unit time of occurrence of a chemical reaction.

write the **master equation** for the rate of change of the **probability** of the system having given concentrations of reactants and products

The Stochastic Model: The Master Equation

$$\frac{\partial P(\vec{x},t)}{\partial t} = V \sum_{\vec{y}} [T(\vec{x}|\vec{y})P(\vec{y},t) - T(\vec{y}|\vec{x})P(\vec{x},t)]$$

The probability to find the system at state x at time t

The transition rate from the state y to state x

The Stochastic Model: The Langevin Equation

$$\frac{d\omega}{dt} = \underbrace{-\frac{2k_n k_d V}{N k_a}\omega}_{\text{Deterministic Part}} + \sqrt{\frac{2k_d}{N}(1-\omega^2)}\underbrace{\eta(t)}_{\text{White noise}}$$

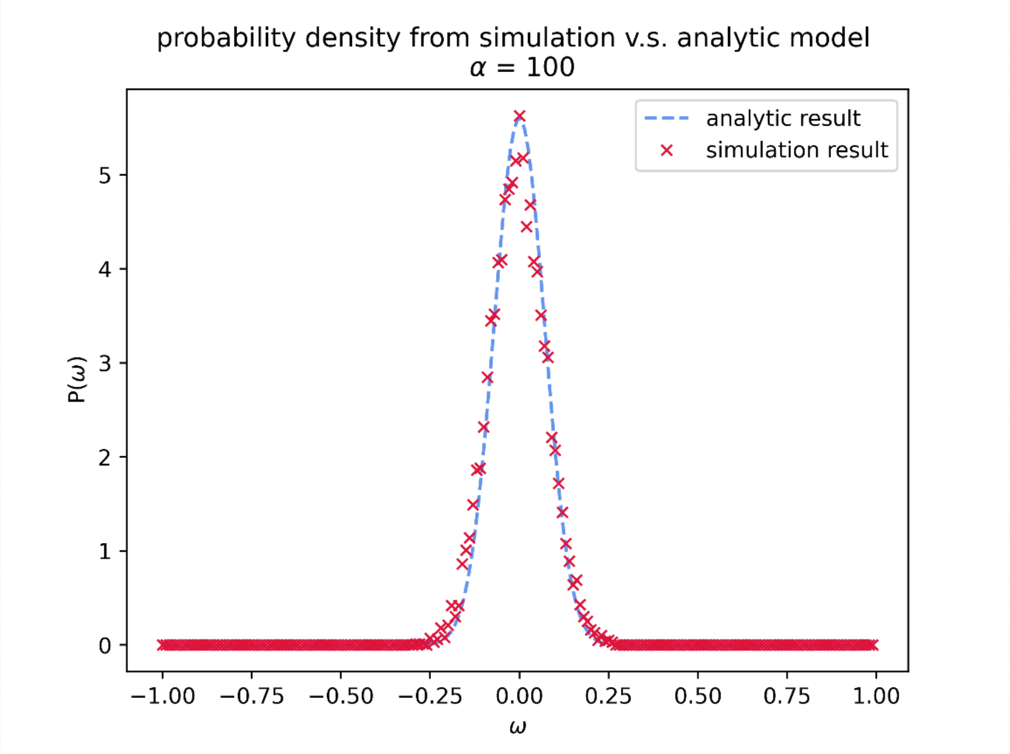
The Stochastic Model: The Fokker – Planck Equation

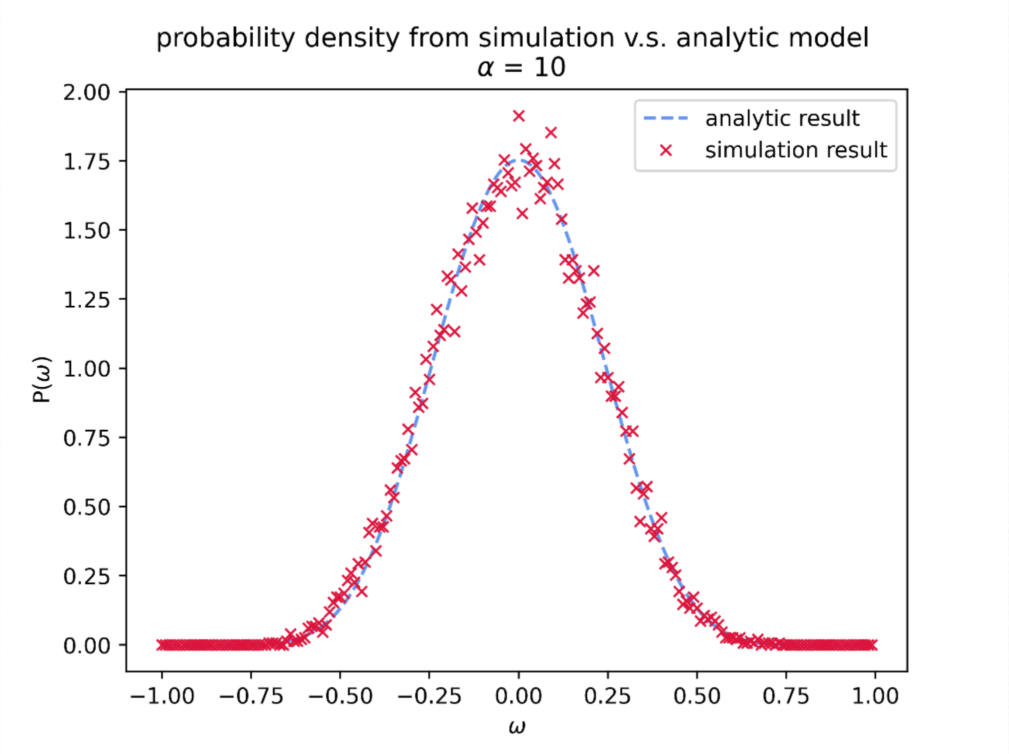
$$\frac{\partial P(\omega,t)}{\partial t} = \frac{\partial}{\partial \omega}\left[\frac{2k_n k_d V}{N k_a}\omega P(\omega,t)\right] + \frac{1}{2}\frac{\partial^2}{\partial \omega^2}\left[\frac{2k_d}{N}(1-\omega^2)P(\omega,t)\right]$$

The Steady State Solution

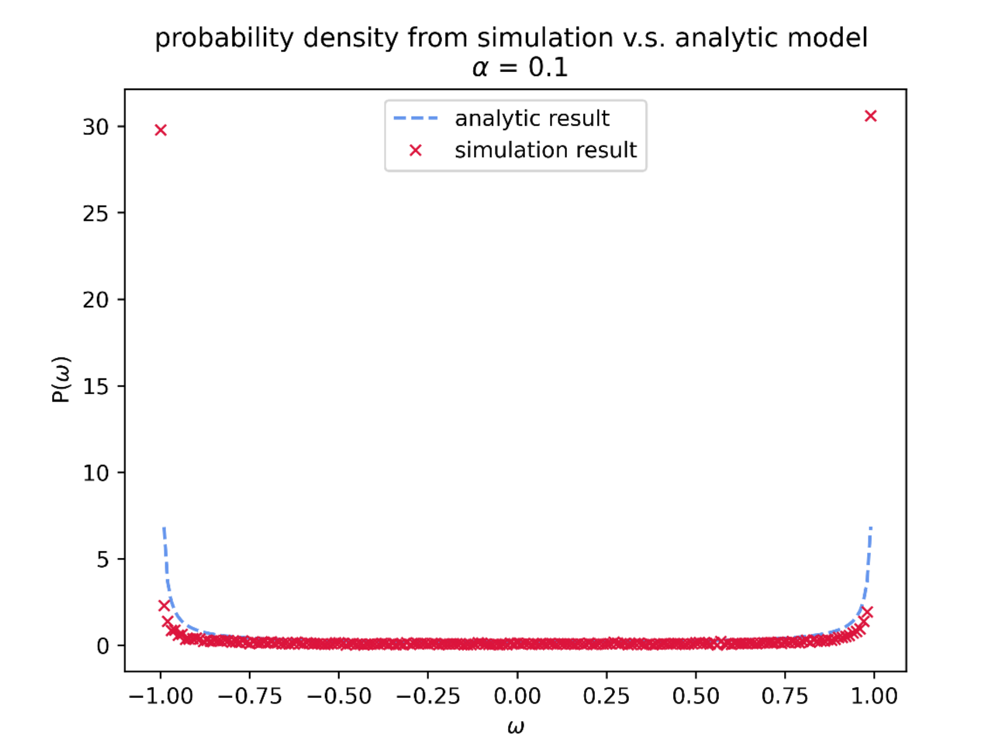
$$P_s(\omega) = \mathcal{N}(1-\omega^2)^{\alpha-1}, \quad \text{with} \quad \alpha = \frac{k_n V}{k_a}$$

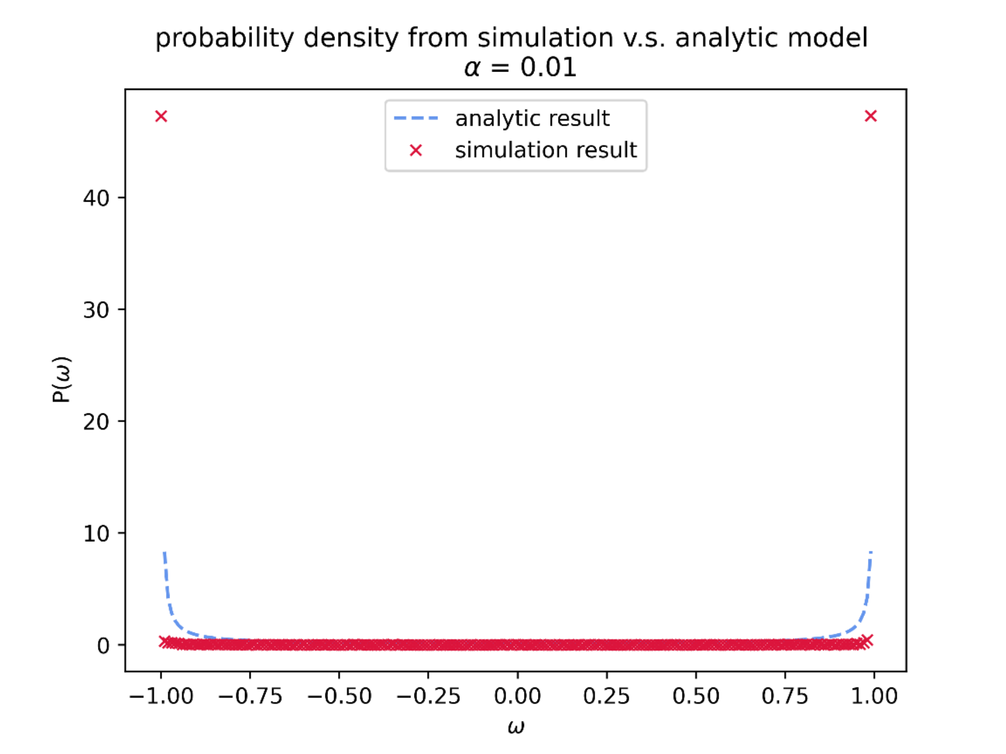
The Stochastic Model: Gillespie simulations for $\alpha > 1$



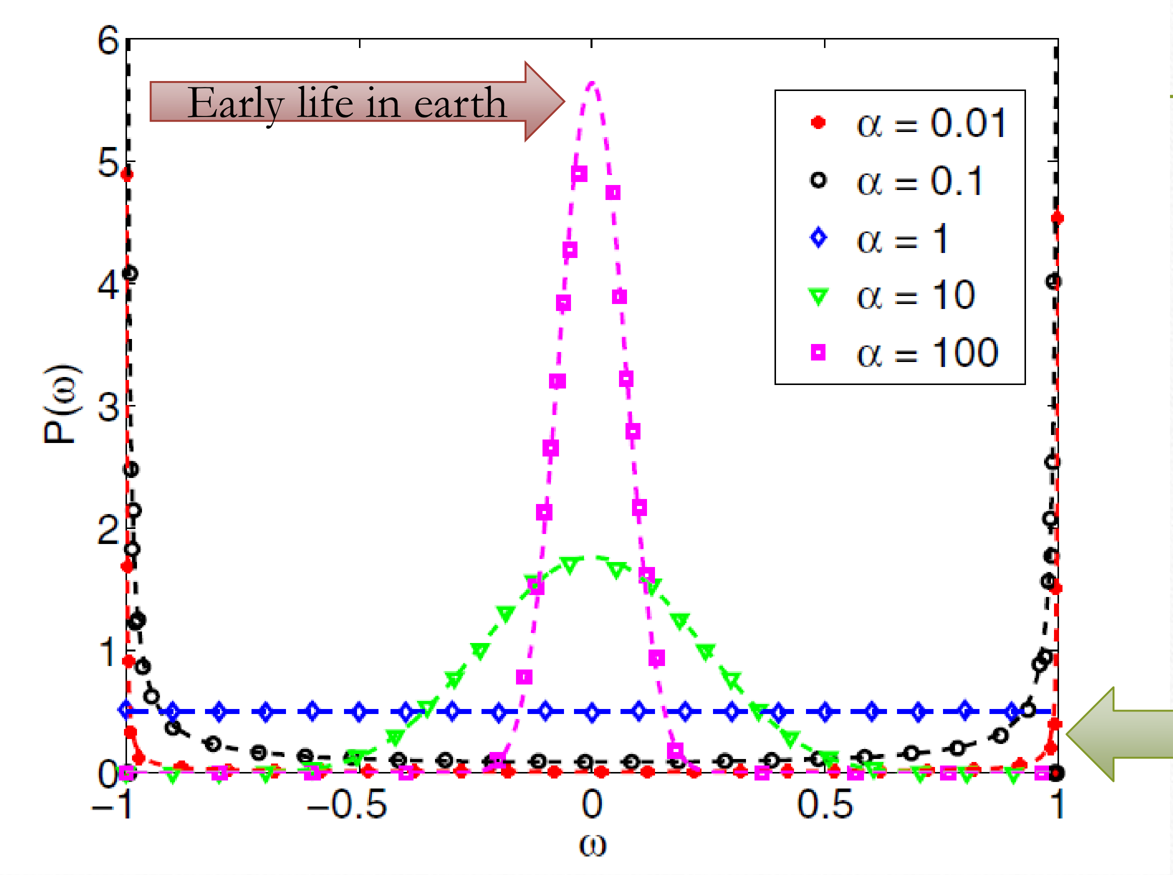


The Stochastic Model: Gillespie simulations for $\alpha < 1$





The Stochastic Model



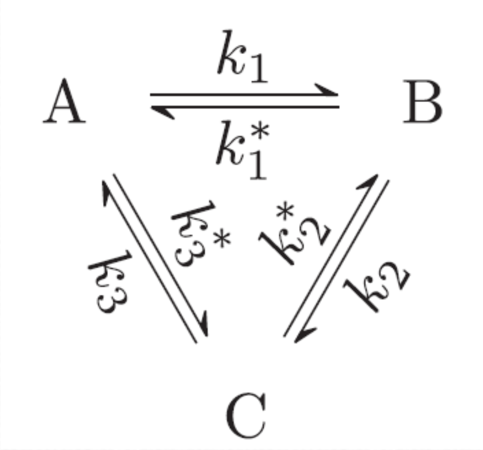
As life evolved

$$\alpha_c = 1$$

The parameter α is proportional to the ratio of the nonautocatalytic production rate, k_n, to the self replication rate, k_a.

Thermodynamics of the System: principle of microscopic reversibility

the **principle of microscopic reversibility** states that **at equilibrium**, the rate of the forward reaction and the reverse reaction are equal for all reactions.



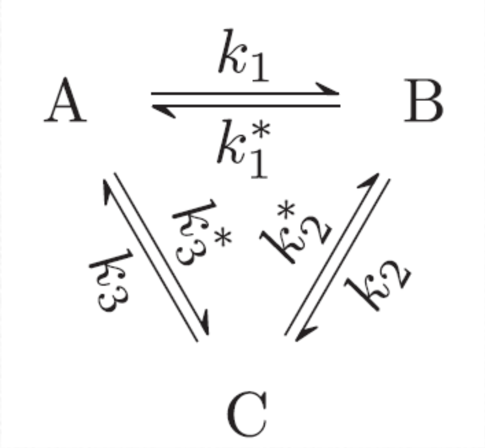
$$k_1[A] = k_1^*[B], \quad k_2[B] = k_2^*[C], \quad k_3[C] = k_3^*[A].$$

Wegscheider's Condition

$$\frac{k_1}{k_1^*}\frac{k_2}{k_2^*}\frac{k_3}{k_3^*} = 1.$$

Thermodynamics of the System: Wegscheider's Condition

The constants are constants! Therefore even away from equilibrium the condition should hold. In other words, Wegscheider's condition is **the condition for the existence of static equilibrium solution**.



$$k_1[A] = k_1^*[B], \quad k_2[B] = k_2^*[C], \quad k_3[C] = k_3^*[A].$$

Wegscheider's Condition

$$\frac{k_1}{k_1^*}\frac{k_2}{k_2^*}\frac{k_3}{k_3^*} = 1.$$

Thermodynamics of the System: Does our system have an equilibrium solution?

$$A + \mathrm{D} \underset{k_a^*}{\overset{k_a}{\rightleftharpoons}} 2\mathrm{D}, \quad A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{D}$$

$$k_a[A][\mathrm{D}] = k_a^*[\mathrm{D}]^2, \quad k_n[A] = k_d[\mathrm{D}]$$

$$\frac{k_a}{k_a^*} = \frac{k_n}{k_d}$$

Thermodynamics of the System: closed-system set of reactions

$$A + \mathrm{D} + ATP \xrightarrow{k_s} 2\mathrm{D} + ADP + P,$$

$$A + \mathrm{L} + ATP \xrightarrow{k_s} 2\mathrm{L} + ADP + P,$$

$$A + \mathrm{D} \xrightarrow{k_s[ATP]} 2\mathrm{D}, \quad A + \mathrm{L} \xrightarrow{k_s[ATP]} 2\mathrm{L}.$$

$$A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{D}, \quad A \underset{k_d}{\overset{k_n}{\rightleftharpoons}} \mathrm{L}.$$

Thermodynamics of the System: what are the evidence?

It is a fact that all biological systems are driven out of equilibrium.

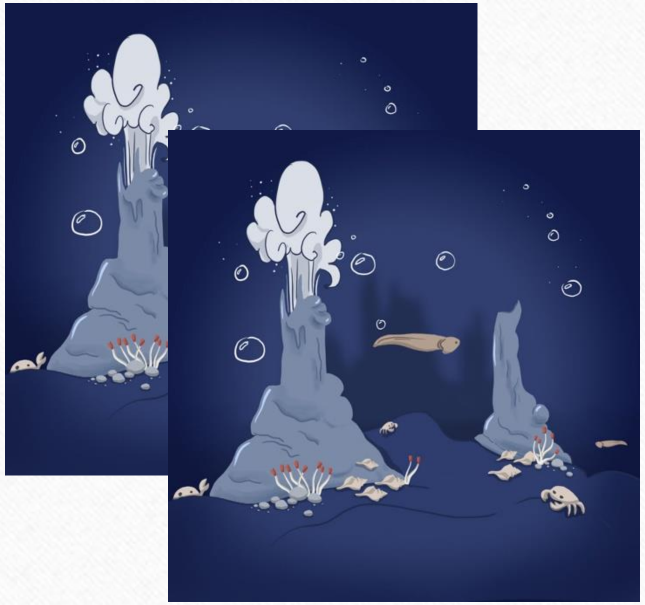
But

There is more reasoning behind the assumption that the homochiral system is driven out of equilibrium:

there is no closed dilute system with a completely homochiral equilibrium.

$$G = U + pV - T\,S$$

Homochirality: The Spatially Extended System



δ: **rate of diffusion** between different sources (for example hydrothermal vents)

- For low values of δ, the chirality of each source is **independent** of the others
- For high values, the sources **synchronize** their chirality.

Homochirality: The Spatially Extended Model

$$A_i \underset{k_d}{\overset{k_n}{\rightleftharpoons}} D_i\,, \quad A_i \underset{k_d}{\overset{k_n}{\rightleftharpoons}} L_i\,, \quad i = 1, \ldots, M$$

# of sources

$$A_i + D_i \xrightarrow{k_a} 2D_i\,, \quad A_i + L_i \xrightarrow{k_a} 2L_i\,,$$

$$D_i \overset{\delta}{\rightleftharpoons} D_j\,, \quad L_i \overset{\delta}{\rightleftharpoons} L_j\,, \quad j \in \langle i \rangle.$$

Neighbors of i

Homochirality: The Spatially Extended Model Results

$$\frac{d\omega_i}{dt} = -\frac{2k_n k_d V}{N k_a}\omega_i + \delta \sum_{j\in\langle i\rangle}(\omega_j - \omega_i)$$
$$+ \sqrt{\frac{2k_d}{N}(1-\omega_i^2)}\,\eta_i(t) + \sqrt{\frac{\delta}{N}}\,\xi_i(\vec{\omega},t),$$

correlated Gaussian noise

$M = 2$ Model: different δ regimes

$$\frac{d\omega_i}{dt} = -\frac{2k_n k_d V}{N k_a}\omega_i + \delta \sum_{j\in\langle i\rangle}(\omega_j - \omega_i) + \sqrt{\frac{2k_d}{N}(1-\omega_i^2)}\,\eta_i(t) + \sqrt{\frac{\delta}{N}}\,\xi_i(\vec{\omega},t),$$

δ *should be compared with* $\frac{2k_d\alpha}{N}$

$M = 2$ Model: critical α for low δ regime

for $\delta \approx 0$

$$Q_s(\omega) = \mathcal{Z}(1 - \omega^2)^{\alpha + \frac{\delta N}{2k_d} - 1}$$

$$\alpha_c \approx 1 - \delta \frac{N}{2k_d}$$

$M = 2$ Model: critical α for high δ regime

$$\frac{d\omega_i}{dt} = -\frac{2k_n k_d V}{N k_a}\omega_i + \delta \sum_{j \in \langle i \rangle} (\omega_j - \omega_i) + \sqrt{\frac{2k_d}{N}(1-\omega_i^2)}\,\eta_i(t) + \sqrt{\frac{\delta}{N}}\,\xi_i(\vec{\omega}, t),$$

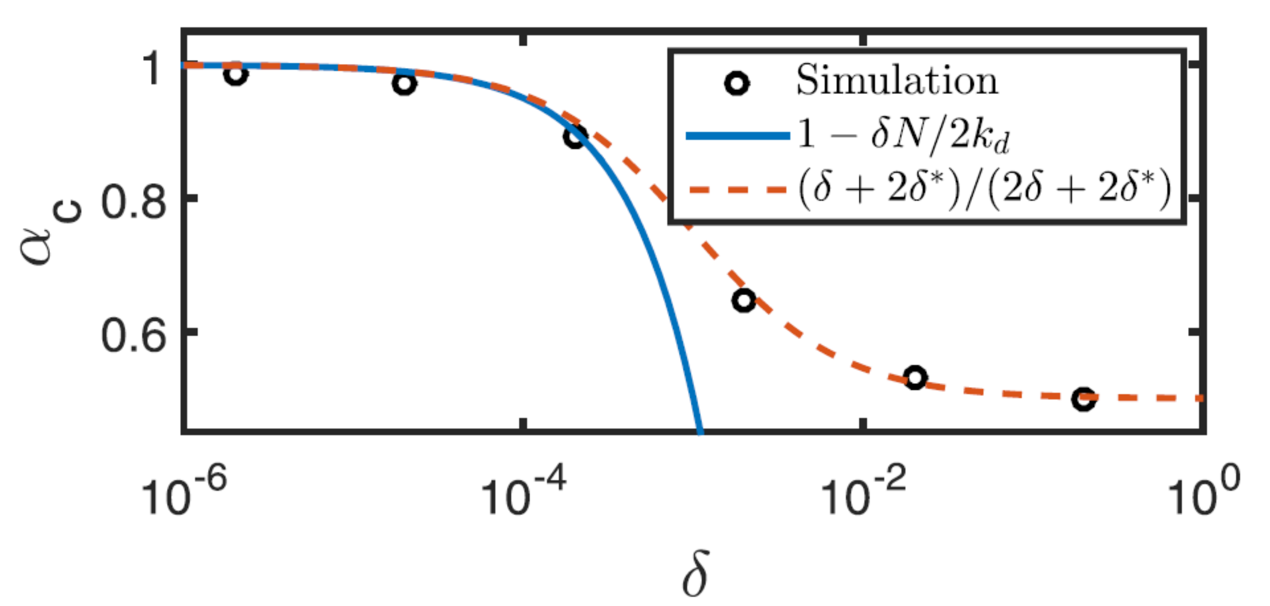
δ *should be compared with* $\frac{2k_d\alpha}{N}$

$$\alpha = \frac{k_n V}{k_a}$$

For $\delta \gg k_d/N$ the whole system can be considered well mixed and has the critical value of α, $\alpha_c^{\text{system}} = 1$, from the well-mixed results

for $\delta \gg 0$. $\alpha_c \approx \frac{1}{2}$

$M = 2$ Model: Robustness Analysis



$$\alpha = \frac{k_n V}{k_a}$$

$$\alpha_c = \frac{\delta + 2\delta^*}{2\delta + 2\delta^*}, \qquad \delta^* = \frac{k_d}{N}.$$

The Spatially Extended Model: Global Homochirality

$$\phi(t,\vec{x}_1,\vec{x}_2) = \langle \omega(t,\vec{x}_1)\omega(t,\vec{x}_2) \rangle$$

$$\zeta = \sqrt{\frac{n\mathcal{D}k_a}{2k_n k_d}}.$$