# Simulating 1-D Amyloid Co-polymerization

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# Introduction

- **Amyloid**: polypeptides which polymerize to form cross-beta structures
- **Co-polymer**: a polymer consisting of two or more monomers (subunits)

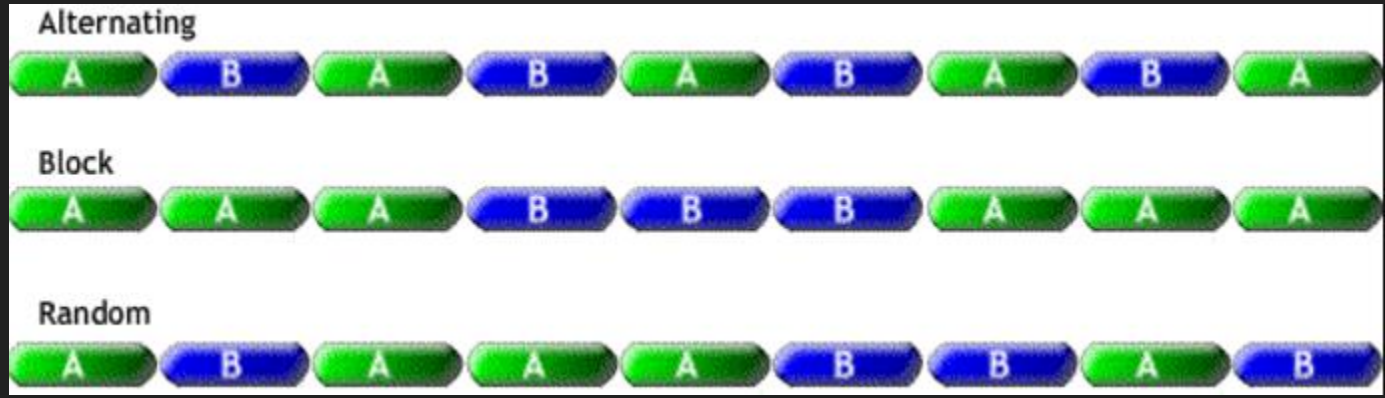
The objective of this project is to simulate a one-dimensional amyloid copolymer consisting of two subunits: **IAPP** (amylin) and **Aβ** (amyloid beta).

**IAPP** is secreted alongside insulin and has been linked to type-II diabetes.

**Aβ** is the main component of amyloid plaques associated with Alzheimer's.

This project builds on work done by Sheena Radford (2017) on IAPP/Aβ amyloid copolymerization, and explores the case in which **binding between dissimilar subunits is stronger** than binding between similar subunits.

# 2 Molecules, 3 Possible Chains and Reactions




- Two molecules, **A** & **B**
- Form linear chain ABAABABBABBAABAAAB…
- Can form Alternating, Block, or Random sequence
- Type depends on interaction energies: $E_{ij}$
- Let I denote the last position in the chain
- Possible reactions: …I→...IA, …I→...IB, …I→..(I-1)

# Algorithm Randomizes Reactions and Timesteps

- Let $K_1$ be reaction rate for addition of A
- Let $K_2$ be reaction rate for addition of B
- Let $K_3 \propto \exp(-E_{ij})$ be reaction rate for last element removal
- Let $K_{tot} = K_1+K_2+K_3$

1. Generate random number: $0<R_1<1$
2. If: { $R_1 \leq K_1/K_{tot}$ : add A to chain ; $R_1 \leq (K_1+K_2)/K_{tot}$ : add B ; else remove }
3. Generate random number: $0<R_2<1$
4. Update timestep defined by: $t \mathrel{+}= -\ln(1-R_2)/K_{tot}$

# Parameter Space Consists of Concentration C, Binding Energy E, and Composition of Solution P

- Define order parameter: $\mathbf{M} = (\mathbf{L})^{-1}\sum \mathbf{s}_i$ from i=1 to i=L where
- **s** = {-1: **A**; +1: **B**} and **L** = length of chain

**M** can be thought of as the composition of the aggregate polymer, and we observe changes in **M** by varying:

- Concentration: **C**
- Binding Energy: **E**
- Ratio of A to B: **P**

**P** can also be thought of as the composition of the solution.

# E=1: Composition of Aggregate Determined by Composition of Solution

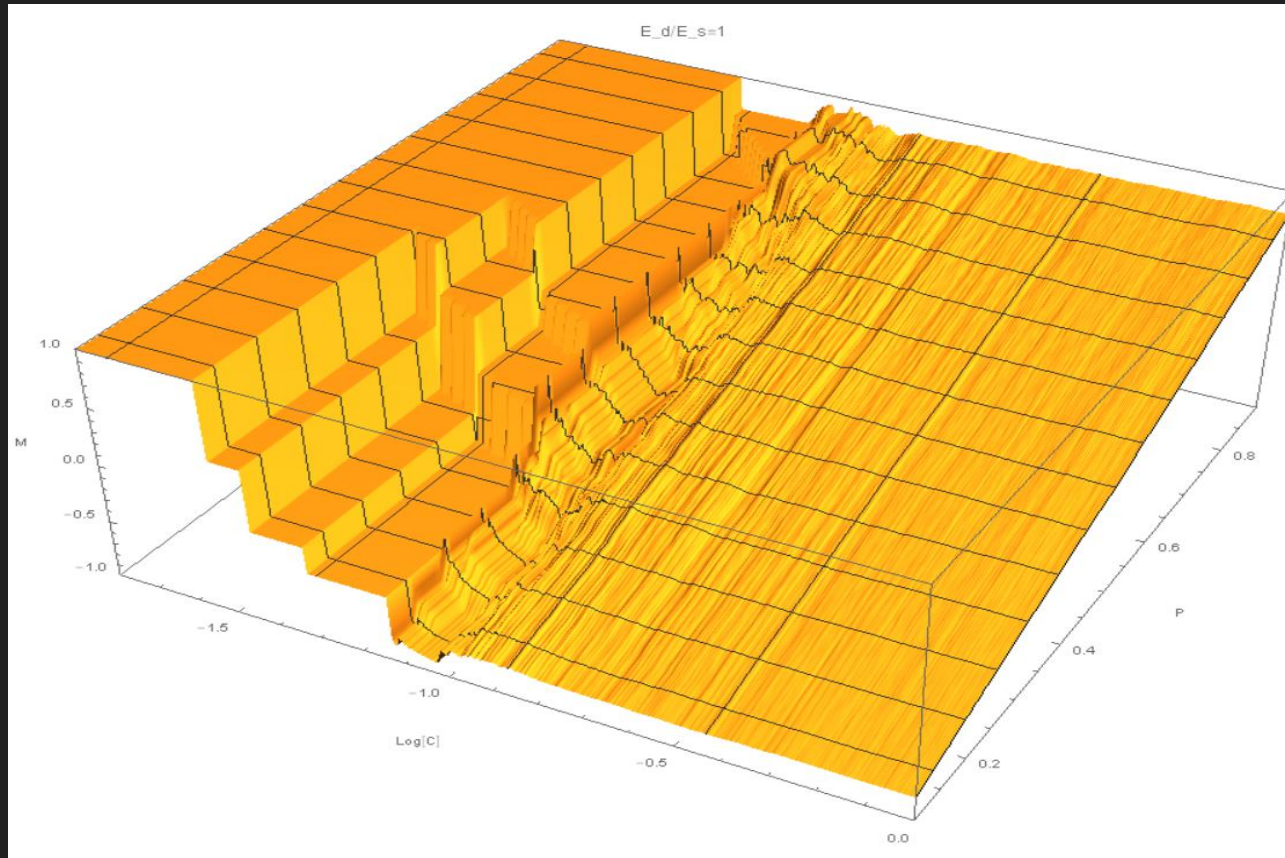
**High Concentrations:**

- M ≈ P

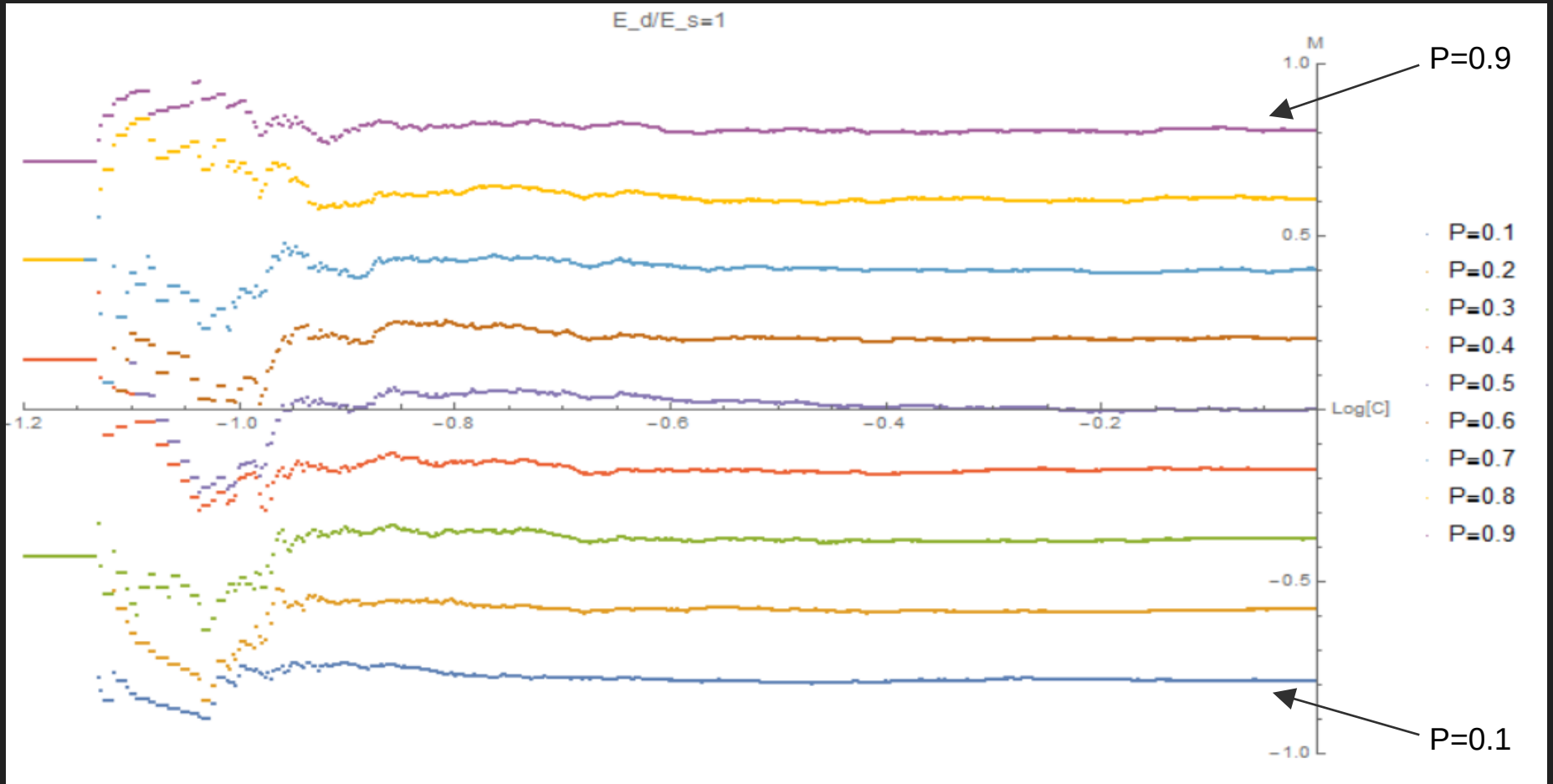
**Low Concentrations:**

- M ≈ P

⇒ **Linear.**



# E=1: Level Sets of P Observed in (M,C) Plane



# E=5: Composition of Aggregate Determined by Binding Energy at Low Concentrations

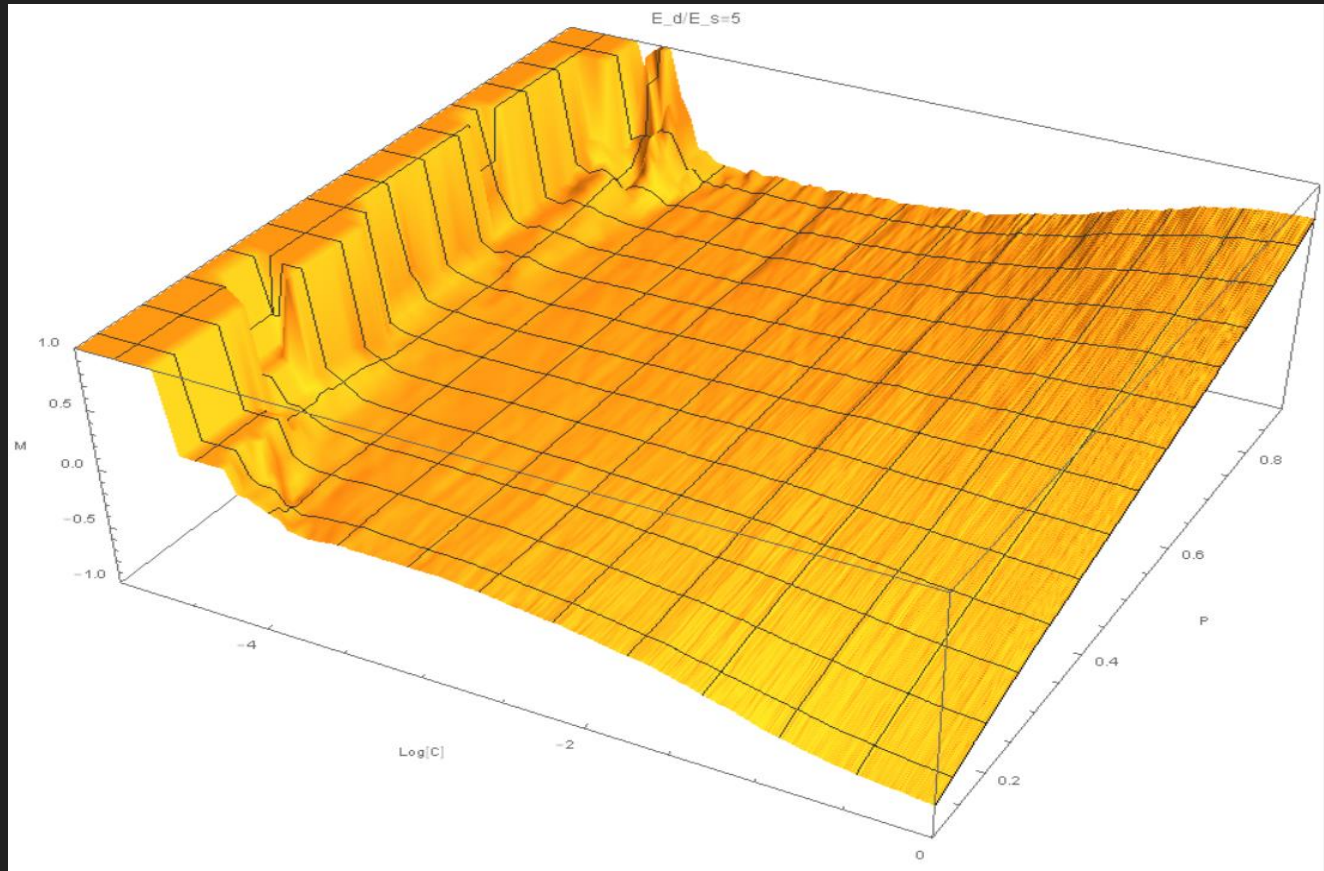
**High Concentrations**

- M ≈ P

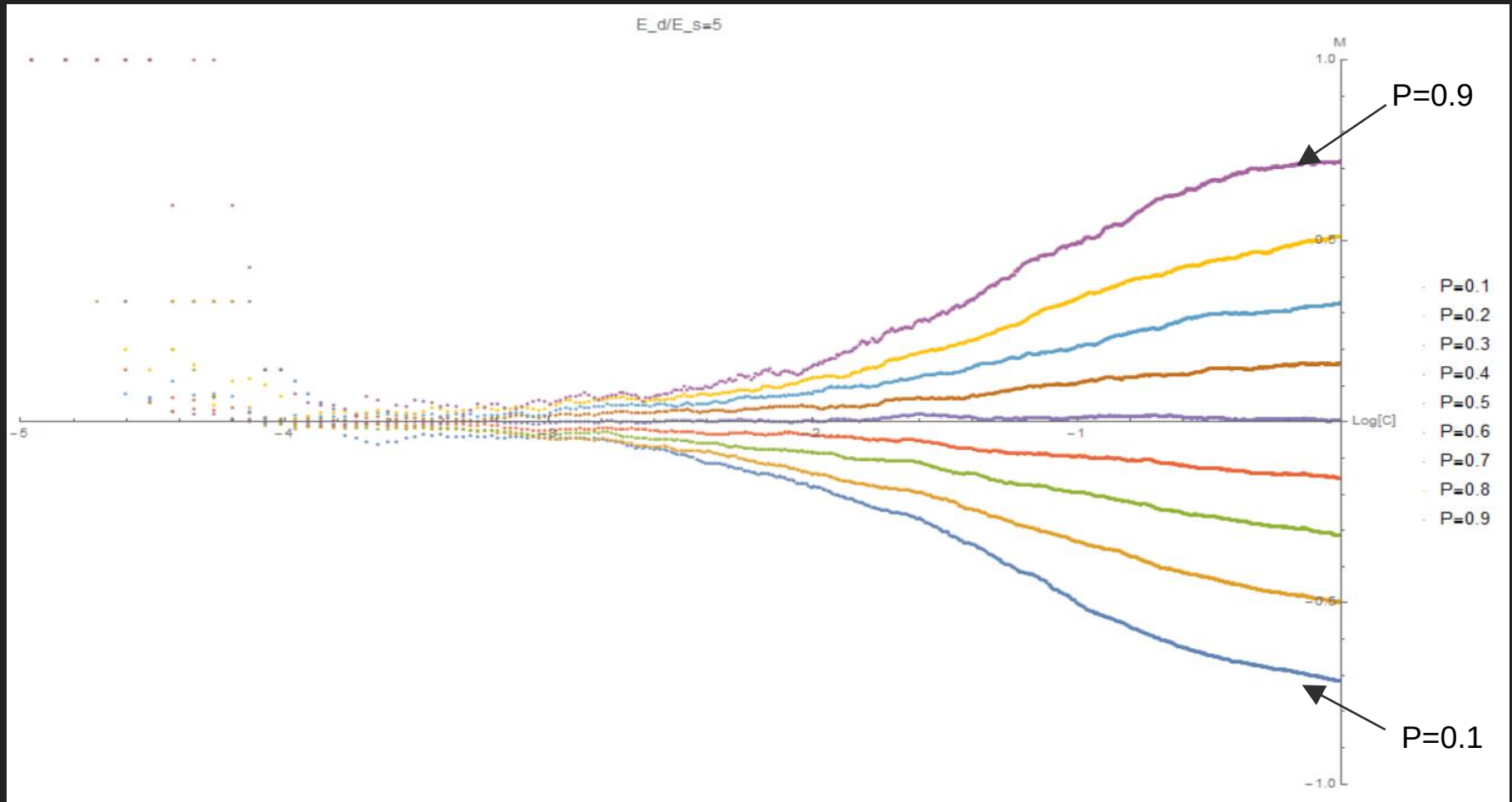
**Low Concentrations**

- M ≈ constant

⇒ **Sigmoidal.**



# E=5: Level Sets of P Observed in (M,C) Plane



# Recap: Composition of Aggregate is a Function of Energy and Concentration

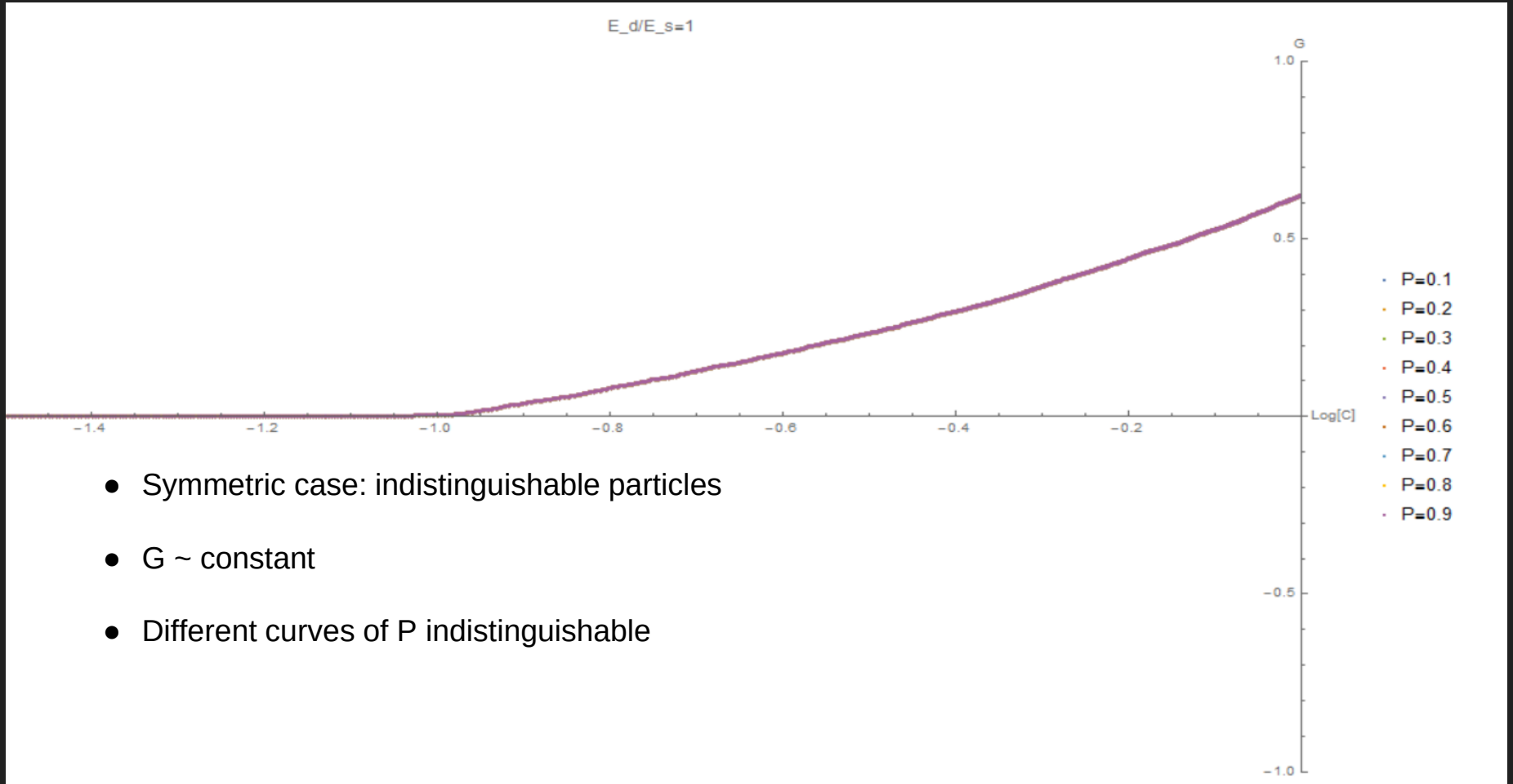
**Small E**:

- Composition of aggregate determined by composition of solution.
- Independent of concentration.

**Large E**:

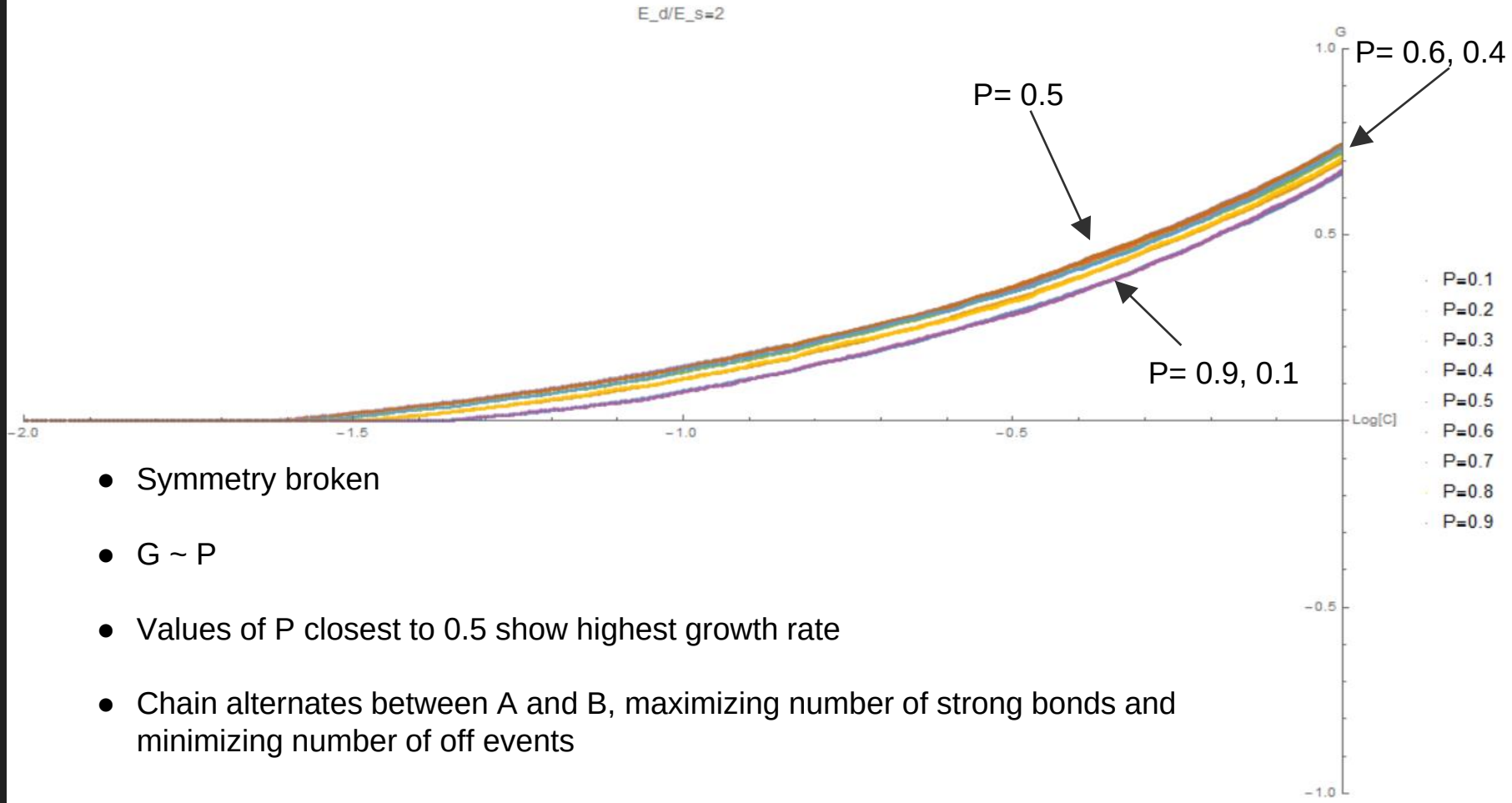
- Composition of aggregate depends on composition of solution only at high concentrations.
- At low concentrations, it is determined by the binding energy.

# E=1: Growth Rate Independent of P



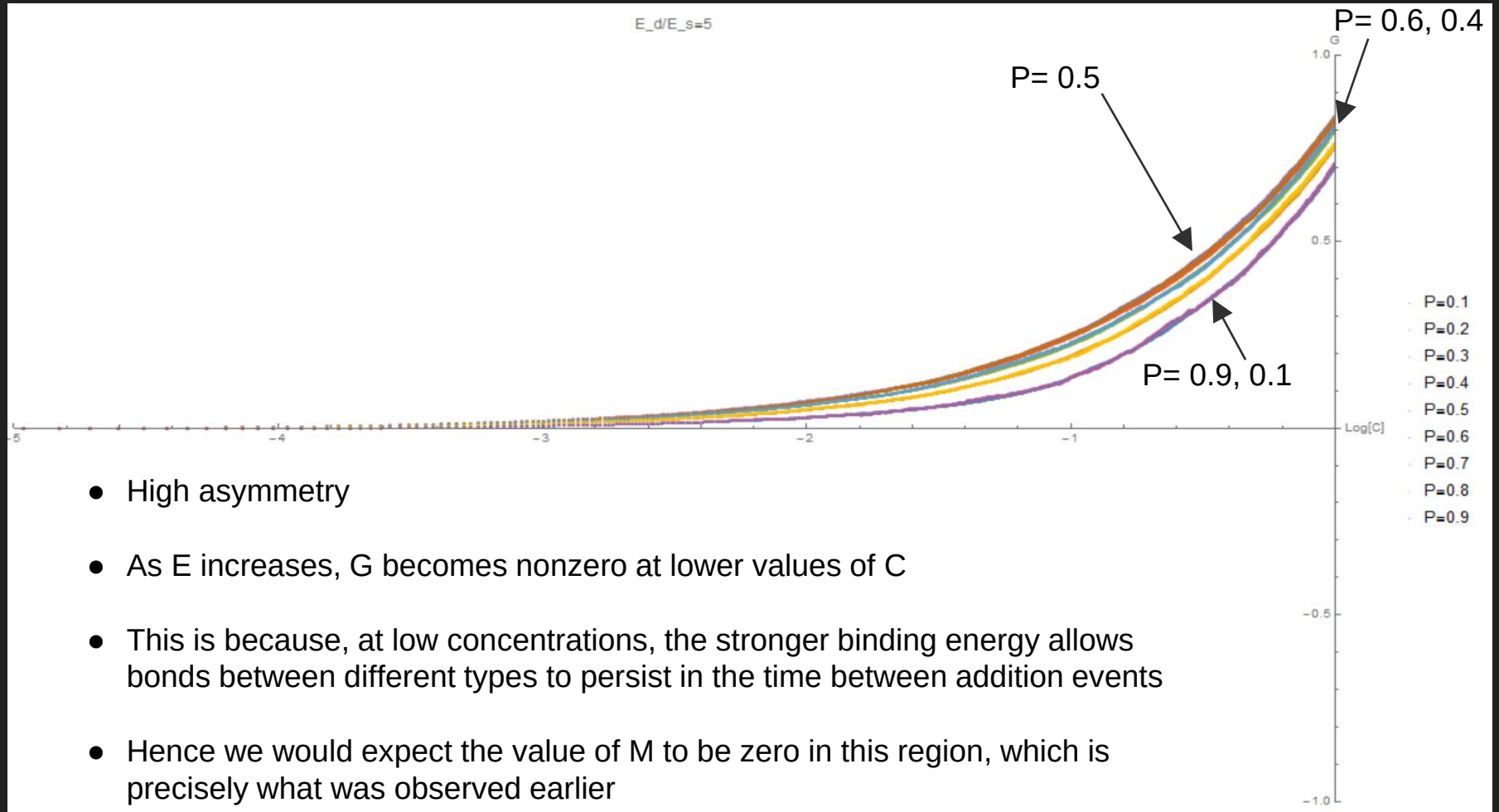

- Symmetric case: indistinguishable particles
- G ~ constant
- Different curves of P indistinguishable

# E=2: Growth Rate Largest Closest to P=0.5



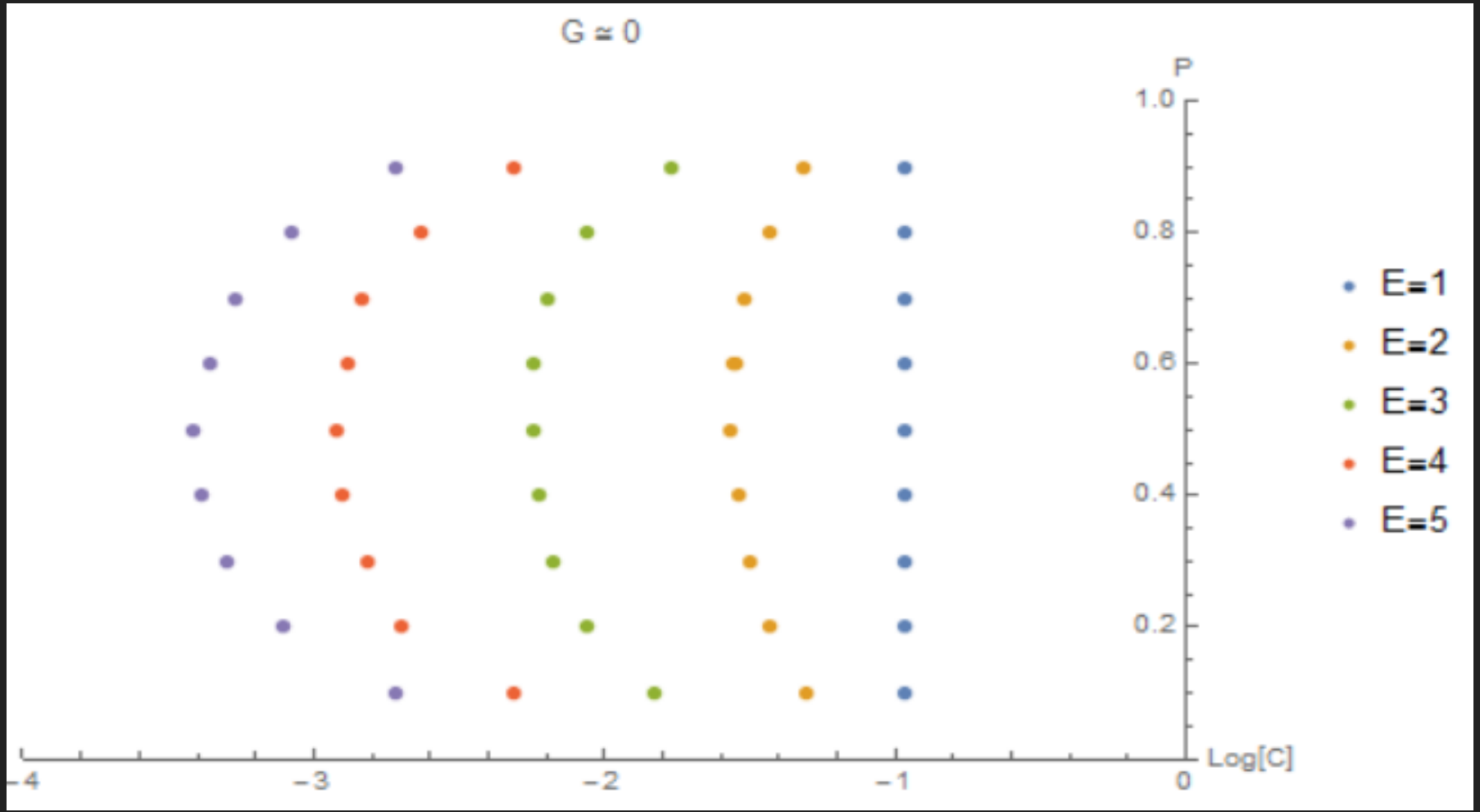

- Symmetry broken
- G ~ P
- Values of P closest to 0.5 show highest growth rate
- Chain alternates between A and B, maximizing number of strong bonds and minimizing number of off events

# E=5: Growth Rate Begins at Lower Concentration




- High asymmetry
- As E increases, G becomes nonzero at lower values of C
- This is because, at low concentrations, the stronger binding energy allows bonds between different types to persist in the time between addition events
- Hence we would expect the value of M to be zero in this region, which is precisely what was observed earlier

# Growth Starts at Lower Concentrations for Higher Energies



# Summary & Future Research

- At high concentrations, chain constituency determined by concentration.
- At low concentrations, chain constituency determined by binding energy.
- Chains with high binding energies begin growing at lower concentrations.
- Future research could account for different masses, charge, and structure.