# Yeast Cell Cycle and Metabolism can be Coupled in Nontrivial Ways

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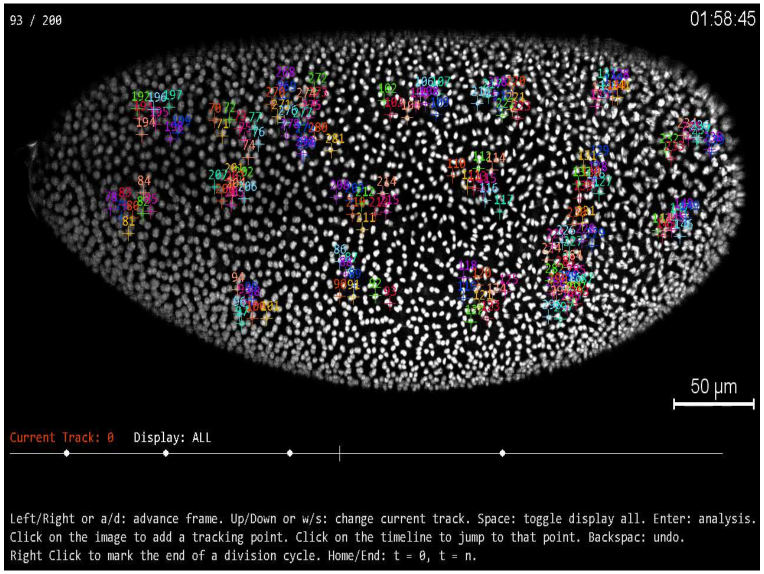
## Synchrony

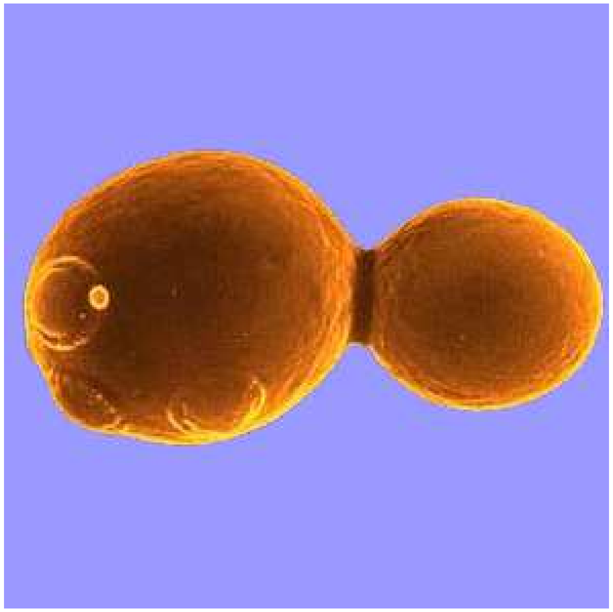



Drosophila embryo:

- Divides synchronously for first 13 divisions.

This is common in Eukaryotes. (Except mammals.)

*Saccharomyces cerevisiae* - Budding Yeast

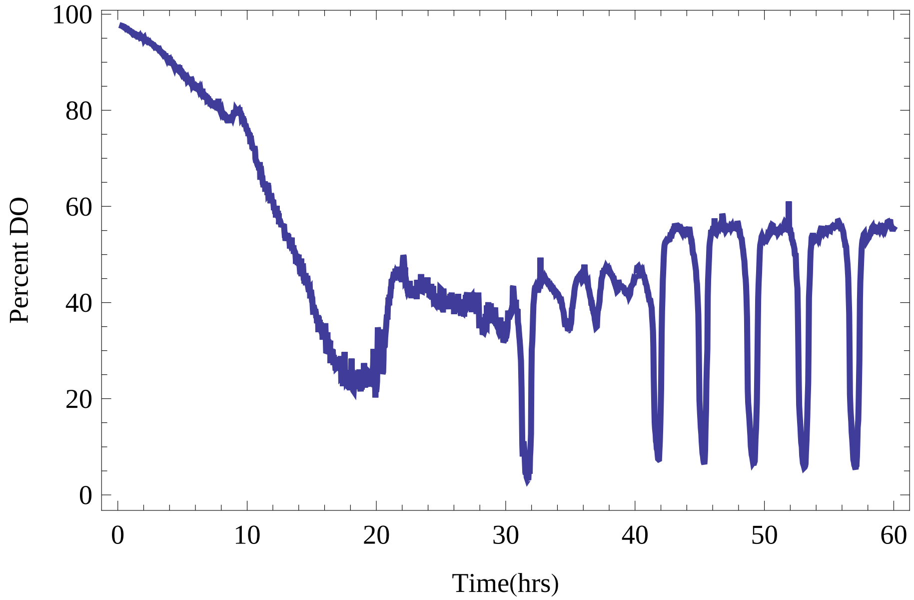


Photos: Wikipedia, www.kaeberleinlab.org, www.alltech.com

Brewer's, Baker's or Ale Yeast. Studied by biologists as a model eukaryotic organism.

Cell cycle synchrony is impossible to sustain in *S. cerevisiae*.

## Yeast Metabolic Oscillations.




A type of synchrony? Yes, metabolic.

A connection between some of these oscillations to the cell cycle was observed long ago, but never explained.

## Temporal Clustering

By *Cluster* we mean a group of cells traversing the cell cycle in near synchrony. (Not spatial clustering.)

**Hypotheses:**

A large cluster of cells in one part of the cell cycle might influence the progress of cells in another part (via metabolic products?).

This feedback can reinforce the formation of clusters.

Clustering and Oscillations are intrinsically linked.

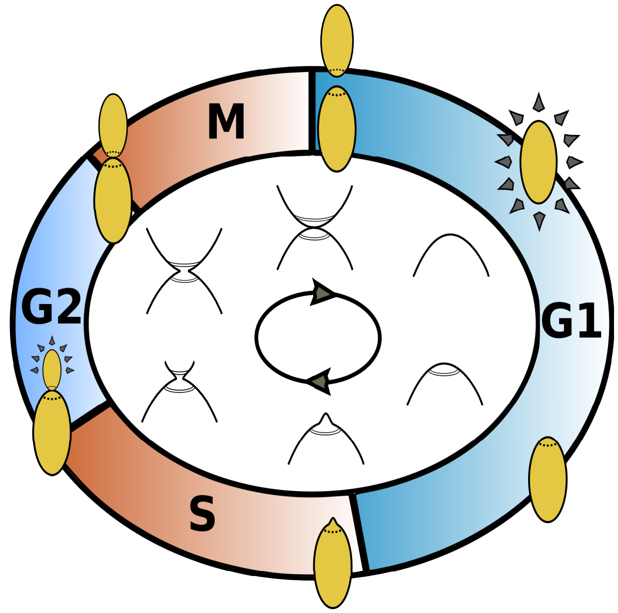
# Cell Cycle of Budding Yeast

G1: growth phase, begins
with cell division

S: replication phase,
begins with budding

G2: second growth phase

M: narrowing or “necking”,
ends in cell division




- *Different, complex* chemistry in each phase.
- Cells in one phase may produce chemicals that influence cells in another phase.

## Model of the Cell Cycle with Phase-Specific Coupling.

$x_i(t) \in [0,1]$ - state of $i$-th cell, $x_i = 1 \mapsto x_i = 0$ (division).

Signaling region $S = [0, s)$. Responsive region $R = [r, 1)$.

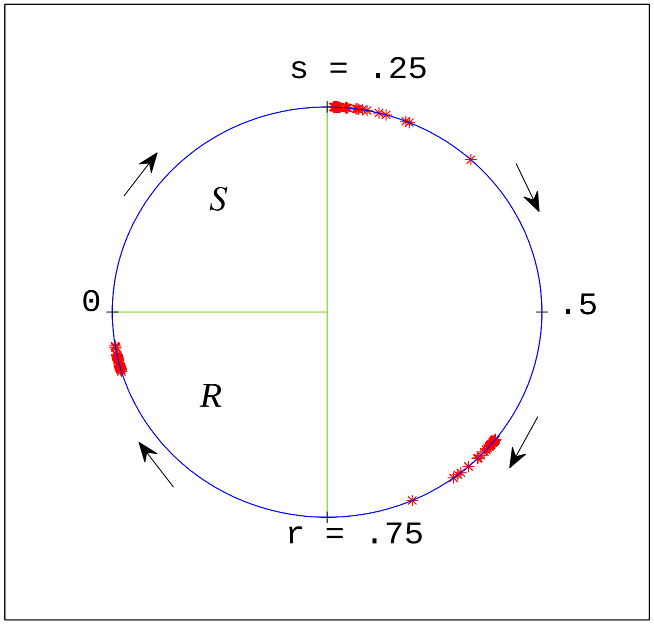
$I = \#\{\text{cells in } S\}/n$.        $n \sim O(10^{10})$ - number of cells.

RS feedback model:

$$\frac{dx_i}{dt} = \begin{cases} 1, & \text{if} \quad x_i \notin R \\ 1 + \rho(I), & \text{if} \quad x_i \in R. \end{cases} \tag{1}$$

$\rho(I)$ - monotone "response" function, $+$ or $-$, *Nonlinear*.

## Clusters Exist - Simulations




500 cells, Negative linear feedback & noise.

R - Responsive
S - Signaling

- Negative RS feedback almost always produces clusters.

## Clusters Exist - Mathematics

In the model (1), a cluster of cells will persist, so we may reduce the dimension to $k$, the number of clusters.

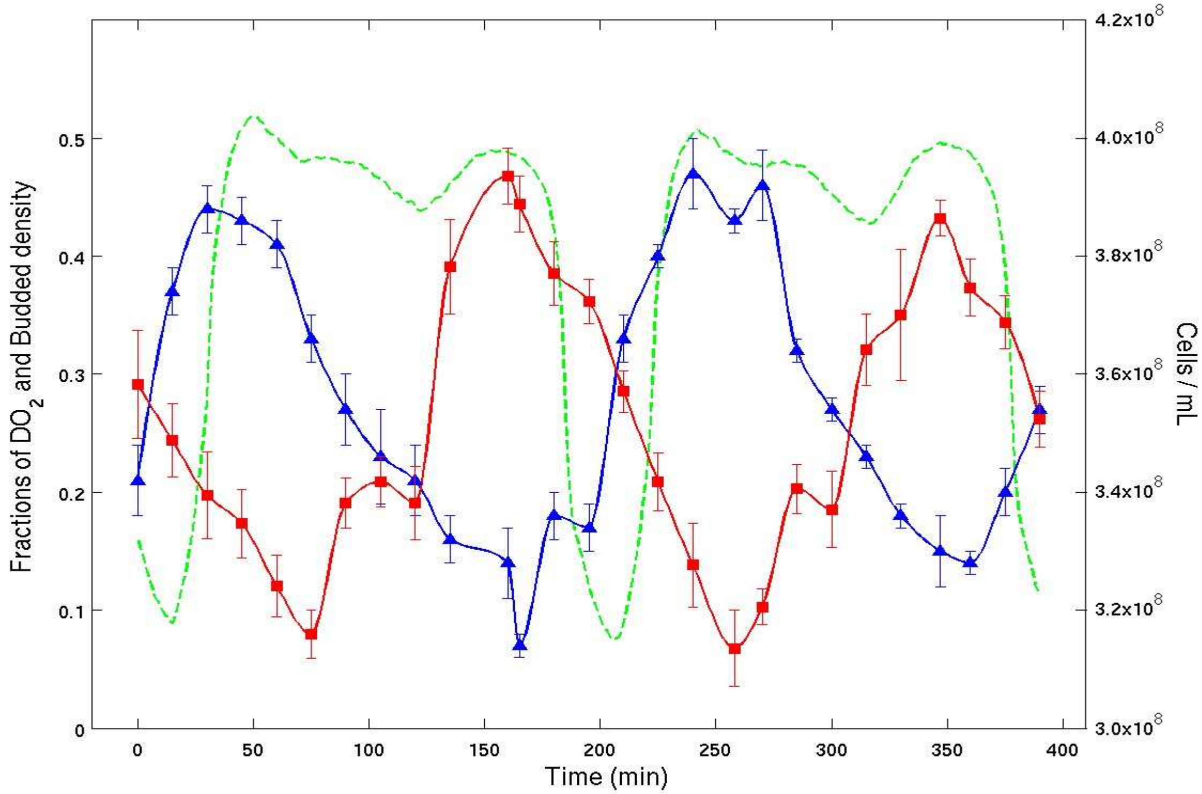
A clustered solution $\{x_i(t)\}_{i=1}^k$ is $k$ **cyclic** if $\exists$ a time $d > 0$ s.t.:

$$x_i(d) = x_{i+1}(0) \quad \forall \quad i = 1, \ldots, k-1,$$
$$\text{and} \quad x_k(d) = x_1(0) \quad \text{mod } 1.$$

**Theorem.** If $k$ is a divisor of $n$, then a cyclic $k$ cluster solution exists consisting of $n/k$ cells in each cluster.

Special Cases: $k = 1$ - *synchronized*. $k = n$ - *uniform*.

## Clusters Exists - Experiments.




Data from Yeast. Oxygen dilution (green), bud index (blue) and cell density (red) over one cell cycle period. There are 2 clusters.

**New questions:**

What are the differences between systems that Synchronize and those that Cluster?

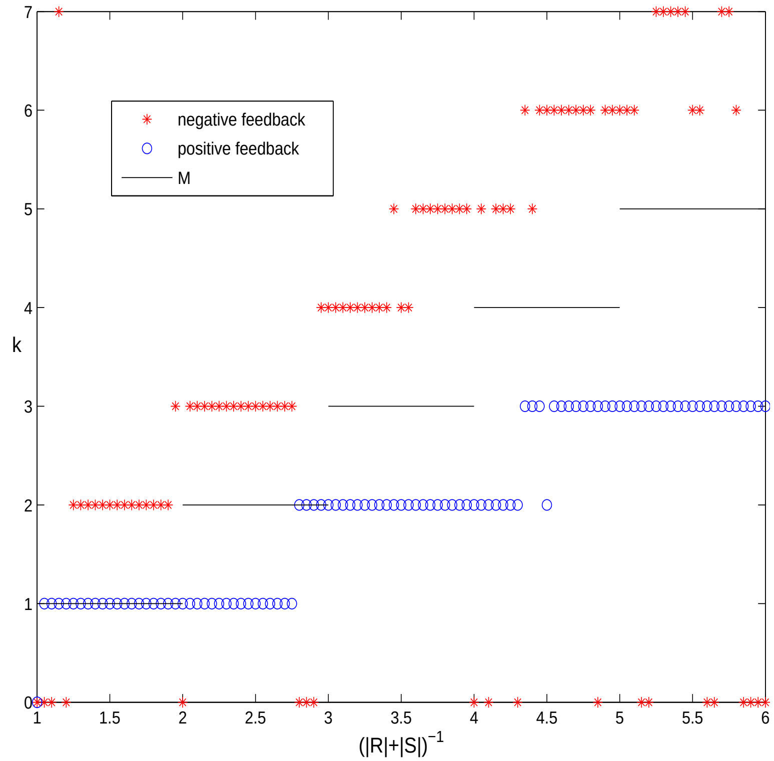
If clusters exist, why don't we often observe them?

What determines how many clusters form?

Generally, things are observed only if they are *Stable*.

Or even better - *Asymptotically Stable.*

# Negative vs. Positive Feedback

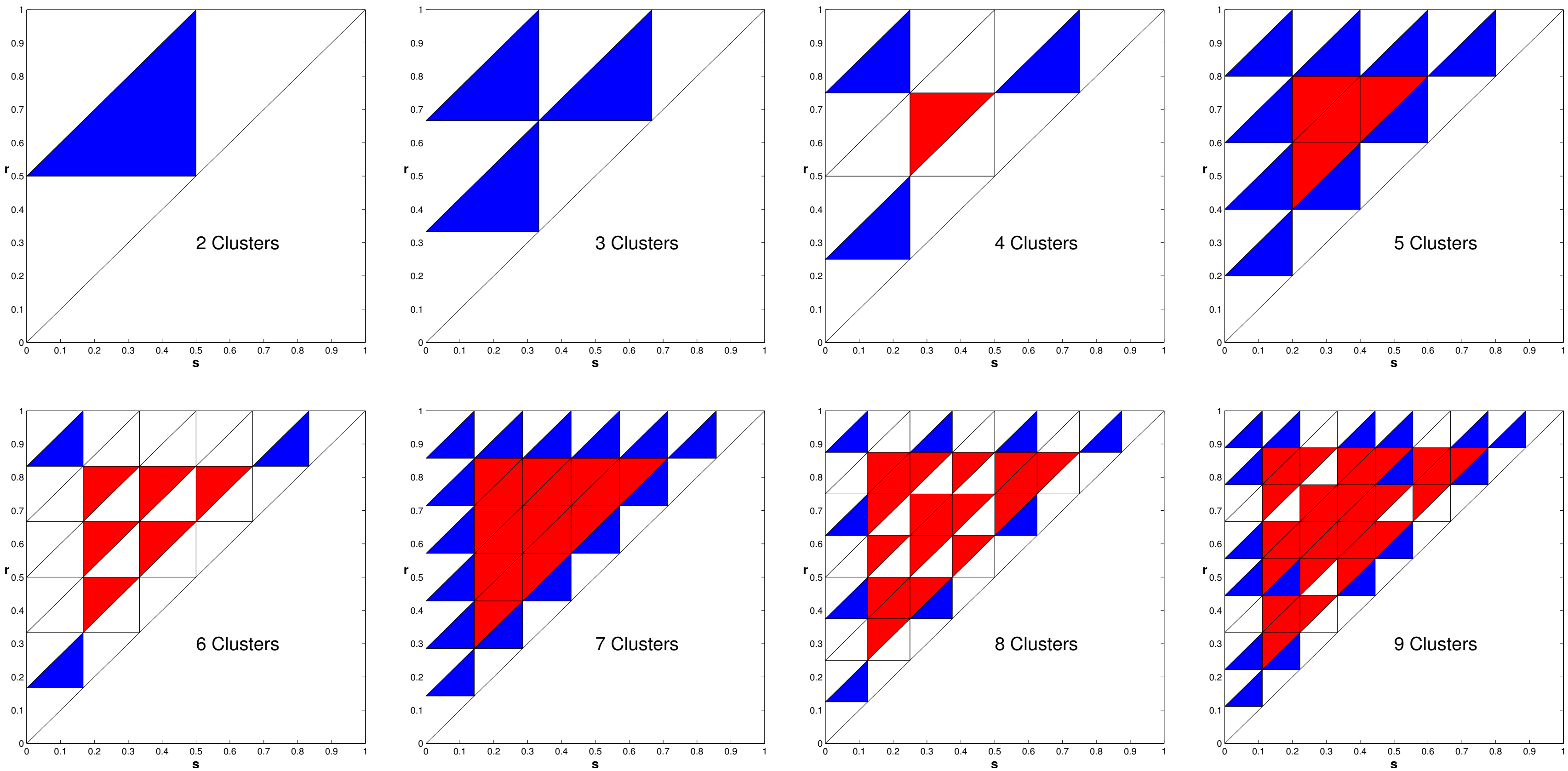



The number of clusters that form in simulations compared with $M = \lfloor (|R| + |S|)^{-1} \rfloor$. $M$ is the number of clusters that can exist without interactions. Stable clustering requires negative feedback and interaction between clusters.

## The Stability of the Synchronized Solution.

**Theorem 1:** In full phase space, the synchronized solution is:
(a) Positive Feedback - asymptotically stable,
(b) Negative Feedback - unstable.

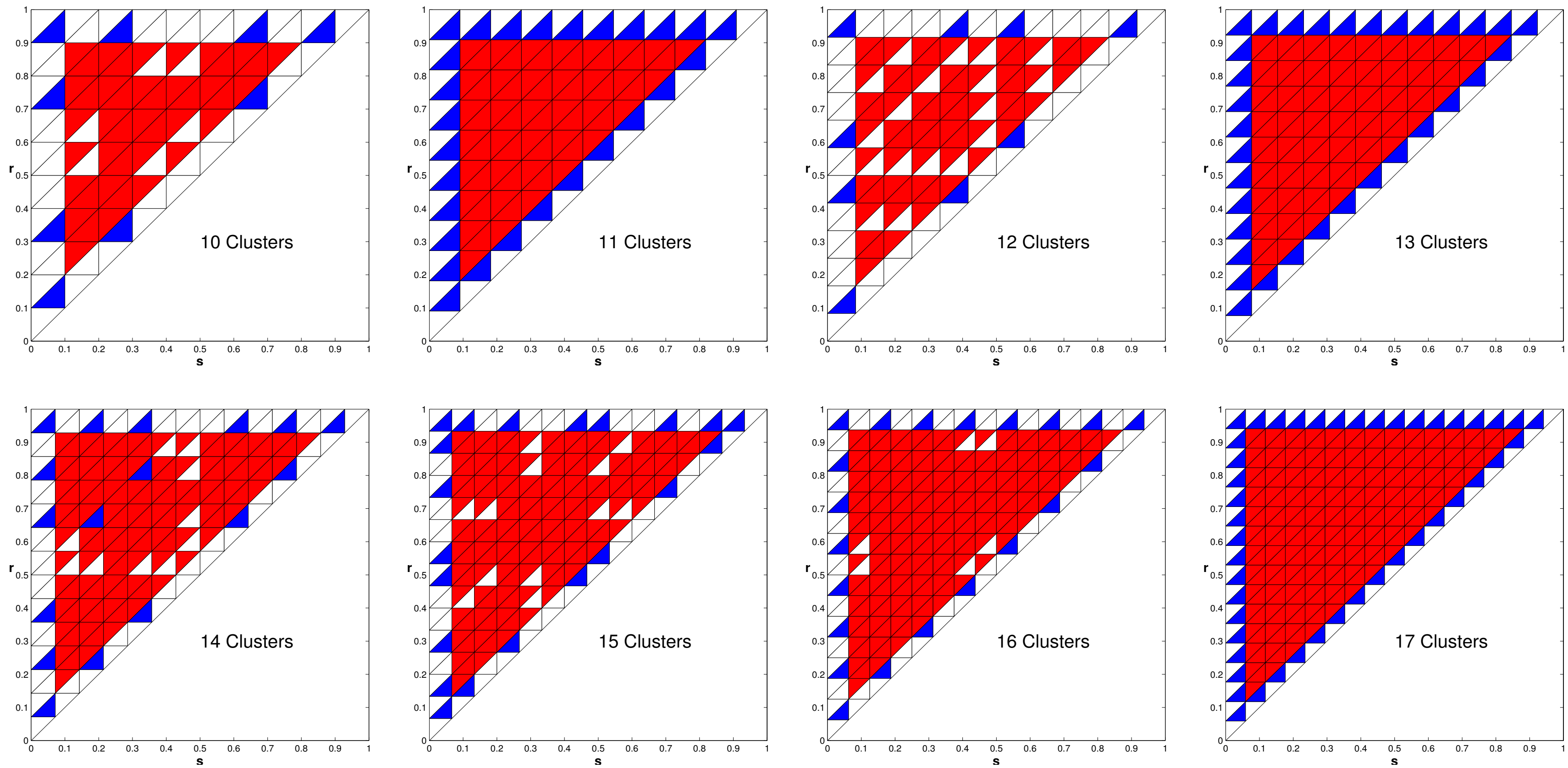
## Stability of $k$ cyclic solution in $r$-$s$ parameter space




Negative Feedback, $k = 2, \ldots, 9$

Blue - Asymptotically Stable, White - Neutral, Red - Unstable.

## Stability of the $k$ cyclic solution in $r$-$s$ parameter space

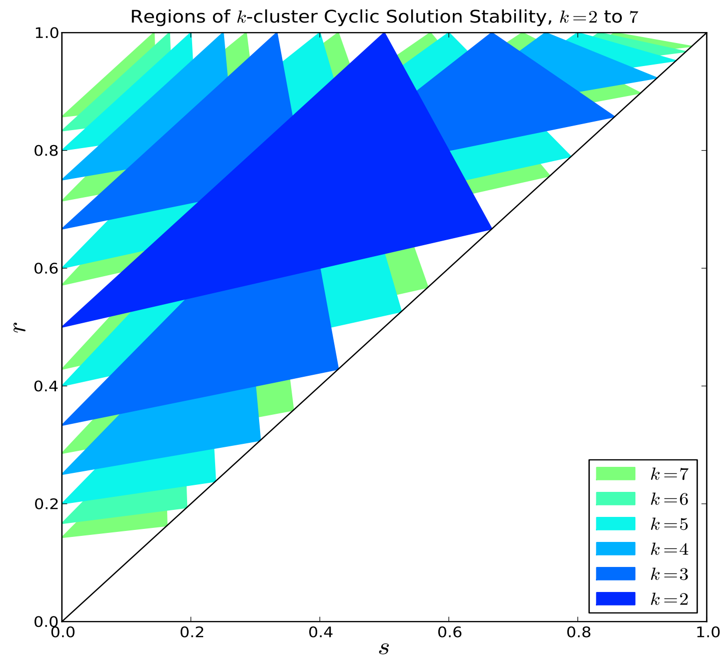



Negative Feedback, $k = 10, \ldots, 17$

Primes are Regular, Composites are Irregular!!.

## Clustering is Universal for Negative Feedback

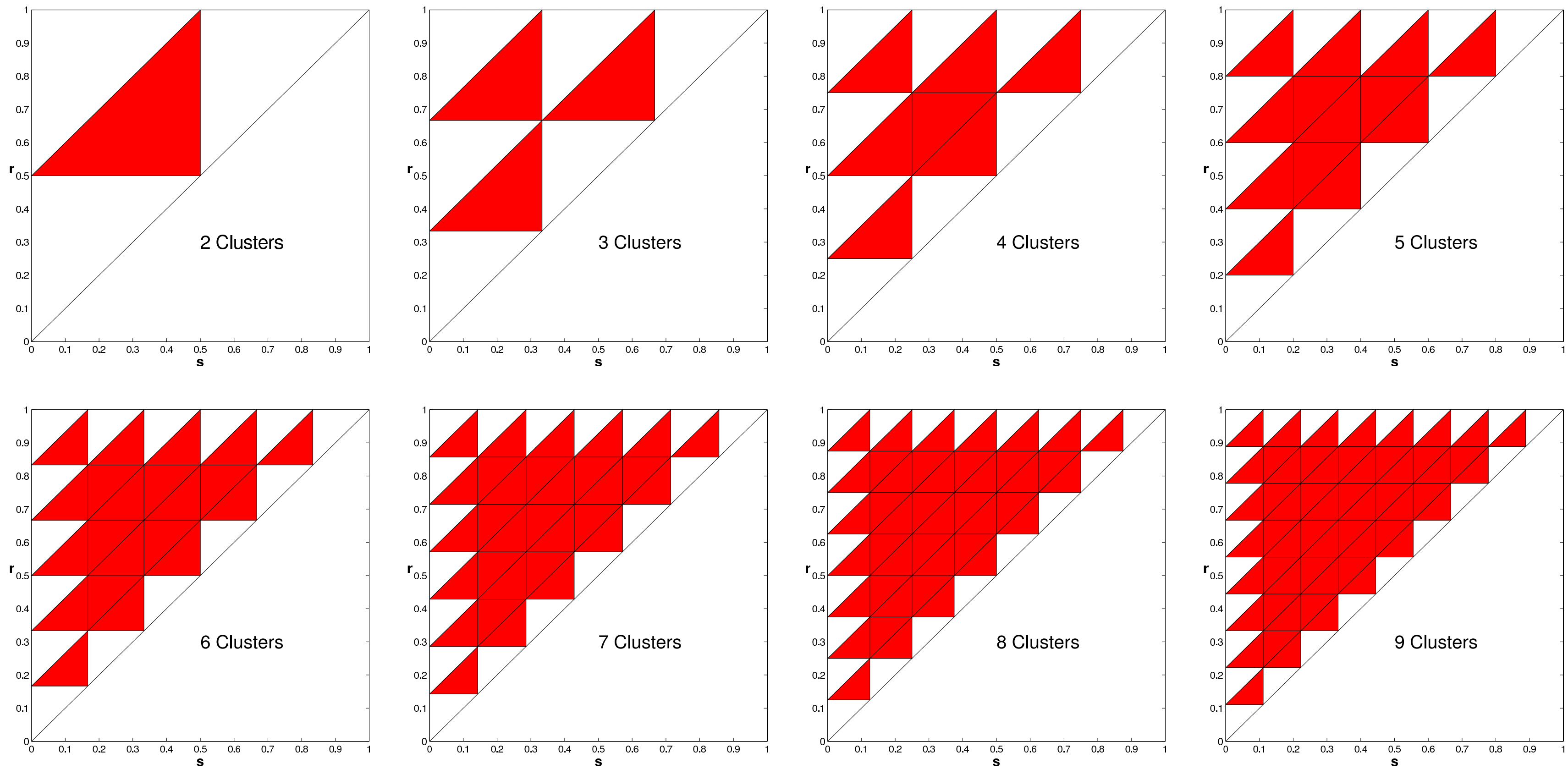
Overlay of Stable Regions:




- *Conjecture:* Every interior point is covered by a stable region for some $k$.

- There are many regions of bi-stability or multi-stability.

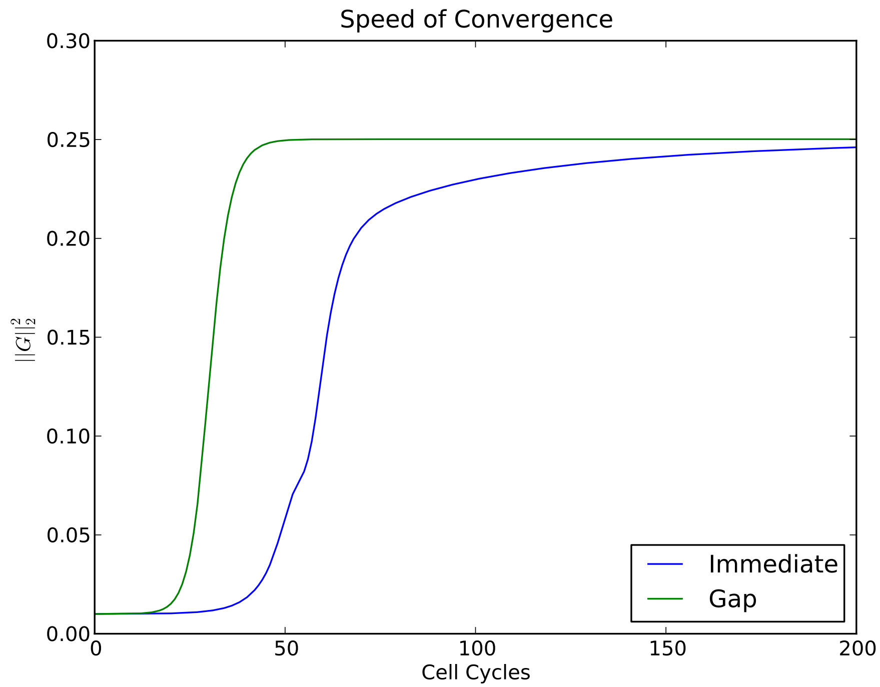
# (in)Stability of Cluster Solutions for Positive Feedback




$k = 2, \ldots, 9$

Multiple Clusters are NEVER Asymptotically Stable.

# Model with a gap (delay)

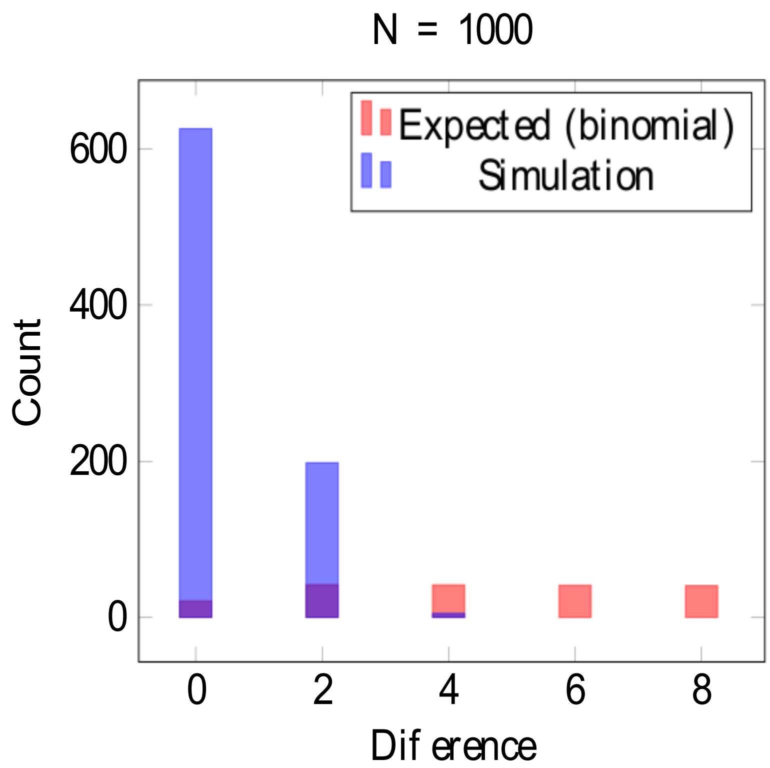



A small delay does not effect the number of clusters.

A delay enhances the stability of stable clusters.

## Clusters Prefer Equity

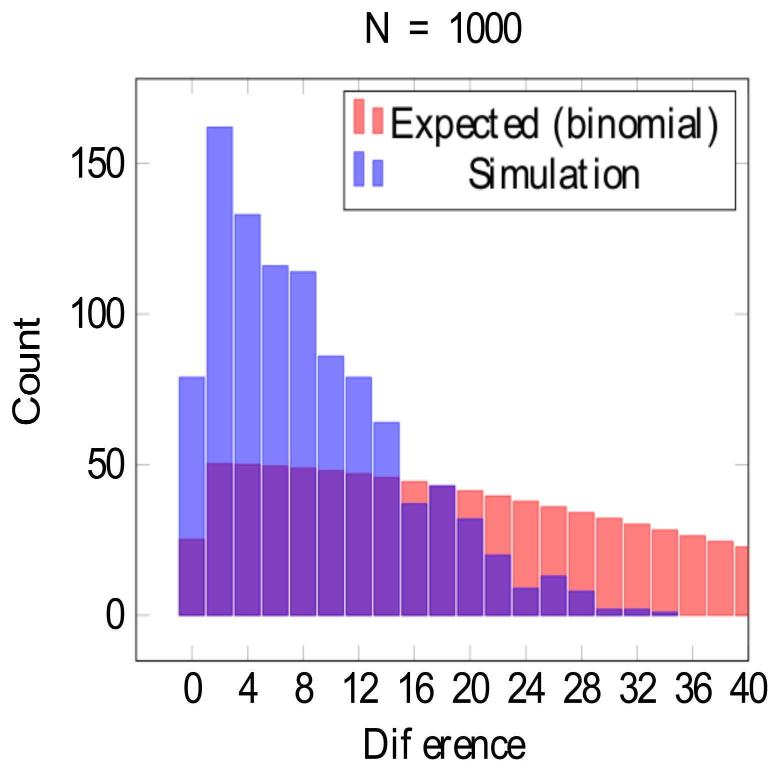
1000 Simulations, 1000 Cells with random initial conditions
Distribution of differences in # of cells/cluster:




Cells are much more equally distributed than they should be.
Local stability is lost when clusters are not equal.

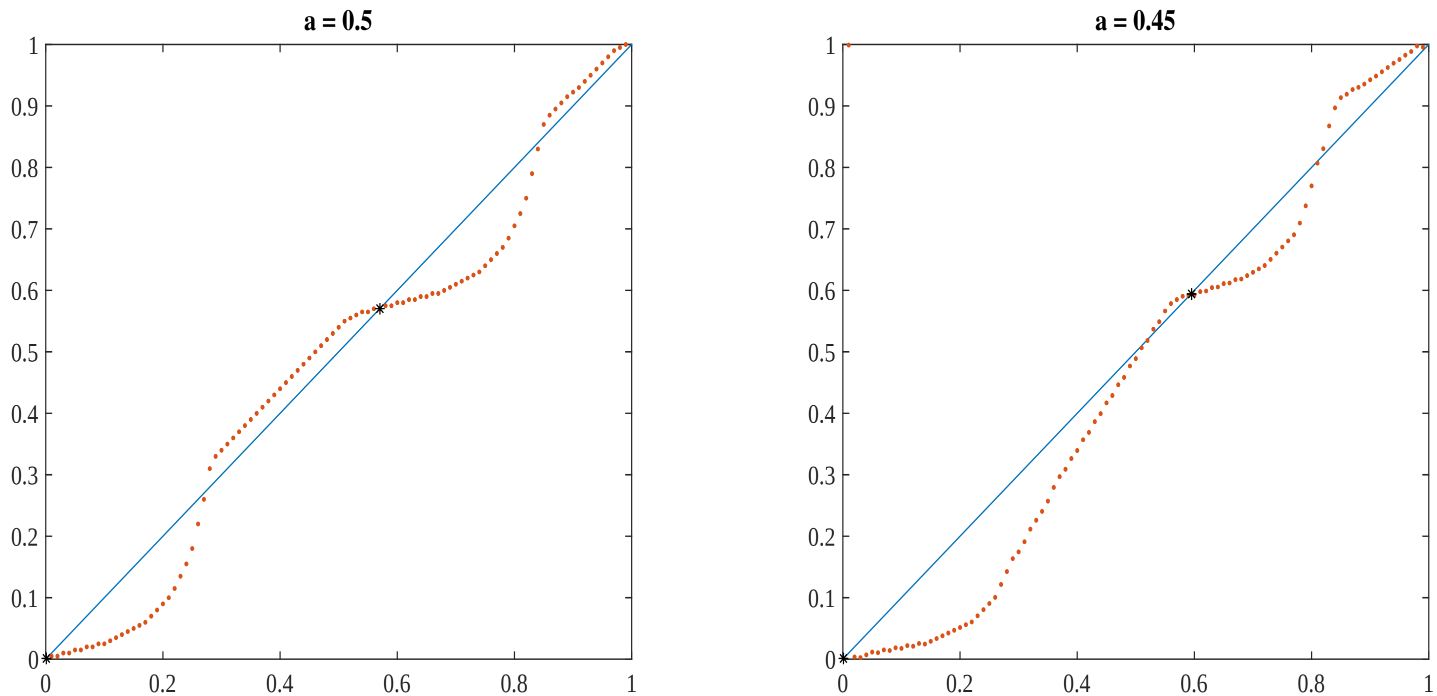
## Model with gap - Clusters Still Prefer Equity

With a small gap, the uneven 2 cluster solution is locally stable, but:




Cells are still more equally distributed than they should be. Why?

# Unequal clusters radically shift the basins of attraction

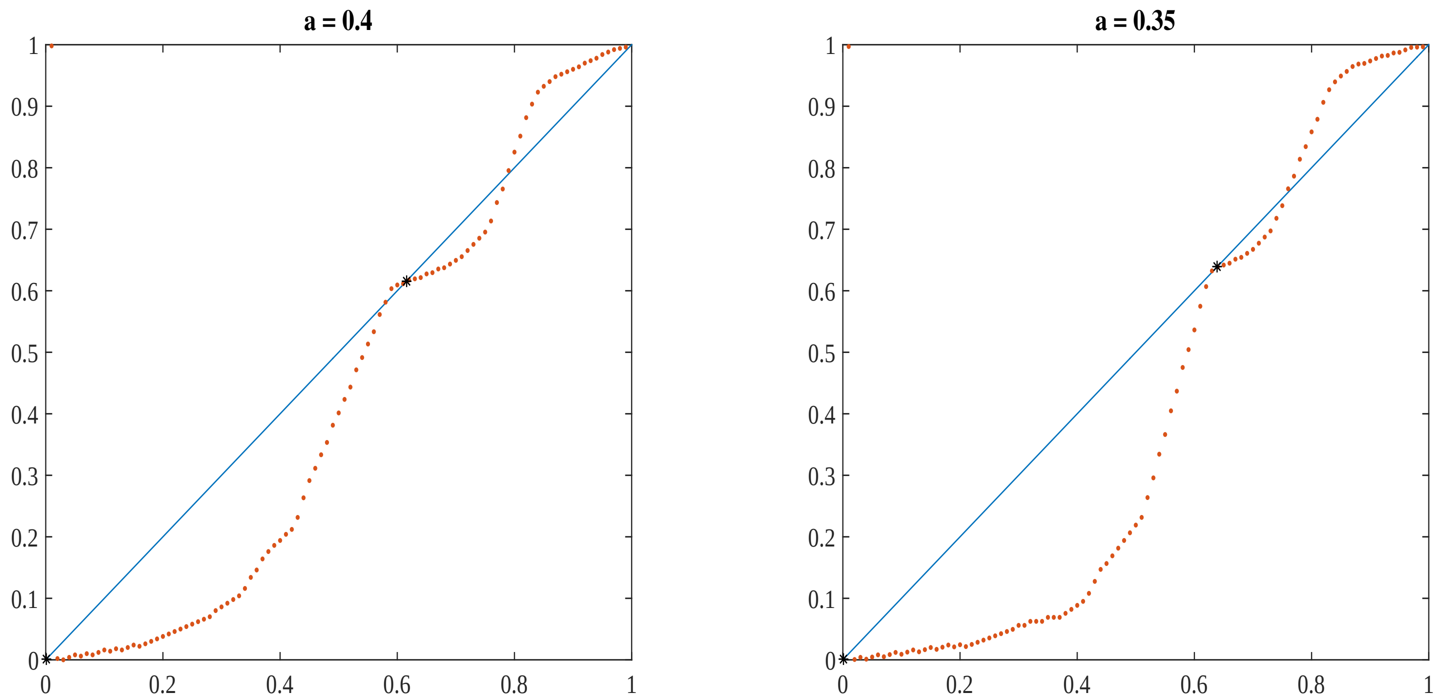



$a \sim$ fraction of cells in cluster 1 (at $x = 0$).

$a = .5$ (evenly distributed) - basins are nearly equal.

$a = .45$ - the small cluster has a much larger basin.

# Unequal clusters radically shift the basins of attraction




Clustering requires interaction. One cluster stabilizes the other.

A large cluster makes the smaller cluster have a larger basin.

## Mathematical Conclusions for General Cell Cycle Feedback

- Systems that Synchronize and Cluster are very different!

- Positive Feedback robustly produces Synchronization.

- Clustering is a robust phenomenon for Negative Feedback:
  - Not dependent on functional form of feedback.
  - It occurs for large open sets of parameter values.
  - It requires interaction among clusters
  - Interaction favors equal clusters

- Number of clusters depends on *size* of $S$ and $R$.