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Systems Chemistry and Parrondo's Paradox: Computational Models of Thermal Cycling

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A mathematical concept known as Parrondo's paradox motivated the development of several novel computational models of chemical systems in which thermal cycling was explored. In these kinetics systems we compared the rates of formation of product under cycling temperature and steady-sate conditions. We found that a greater concentration of product was predicted under oscillating temperature conditions. Our computational models of thermal cycling suggest new applications in chemical and chemical engineering systems.

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Introduction

Systems chemistry is an important niche discipline that investigates the behavior of interacting chemical reactions ( ). Like systems biology and systems engineering, a critical feature of systems chemistry is that unexpected outcomes may arise which may not be predicted form examining the behavior of the individual components of the system. Complex behavior can arise over time from even simple systems. For example, many investigators active in systems chemistry are pursuing the breaking of symmetry that may explain the generation of homochirality in prebiotic environments.

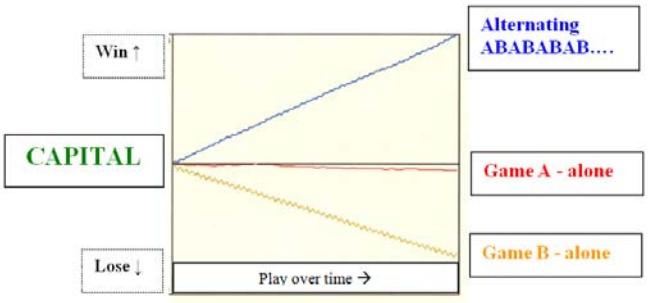
The counterintuitive mathematical concept known as Parrondo's paradox may provide insight into developing chemical model systems in which forced oscillating conditions would give rise to unexpected outcomes. Parrondo's paradox is the unexpected situation in which two specific losing strategies can, by alternating them, produce a winning outcome (1-3). The complex statistical elements of Parrondo's paradox are often demonstrated by means of gambling games. Figure 1 shows the outcome of the most simple form of Parrondo's paradox; in this case, the outcomes of two strategies (Games A or B played alone) are "losing" but if the games are played alternately (ABABAB…) paradoxically the result is a "winning" outcome. A more complete description of the mathematics behind Parrondo's paradox and links to informative animations can be found at The University of Adelaide, School of Electrical Engineering, Official Parrondo's Paradox Page (3).

Parrondo's paradox has generated a significant amount of activity since its presentation in 1999 (4-13). One of the earliest extensions was to use the Parrondo's strategy to develop a

relationship with the paradoxical behavior of Brownian ratchets. The inherent mechanism is described in some physical systems as the "rectification" of "noise" contributing to an unexpected outcome (5,6,8). An interesting variation of a Parrondo's paradox based game was described by Martin and von Baeyer positing that two slowlying winning games could be combined to generate a fast winning game (12). Systems that demonstrate such paradoxical outcomes are understood in terms of the interactions of simple components whereby non-linear, asymmetric behavior emerges. Importantly, applications of Parrondo's paradox do not violate the Second Law of Thermodynamics despite the "something-for-nothing" impression.

Our studies focused on finding a chemical analogy to Parrodo's paradox – discovering a system of hypothetical chemical reactions which might produce a higher yield of a product when switching between conditions compared to steady-state conditions.

Figure 1. The Outcome of a Typical Set of 500 Games
Using the Parrondo's Paradox Strategies for Games A and B, Mod 2



Results and Discussion

A simple stochastic chemical model based on Parrondo's paradox

To mimic the game strategies of Parrondo's paradox, a reaction scheme with the production of alternate products from a common reactant was devised in which product B is considered the "losing" product and C is considered the "winning" product. The reaction could be conducted under Condition I, Condition II or and alternating pattern of conditions, i.e. I II I II I II …..

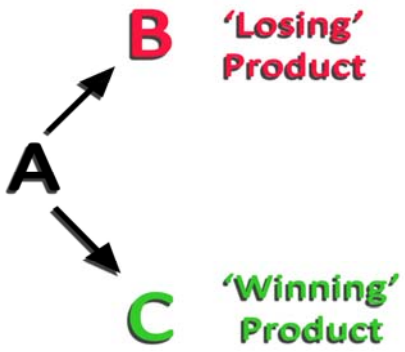


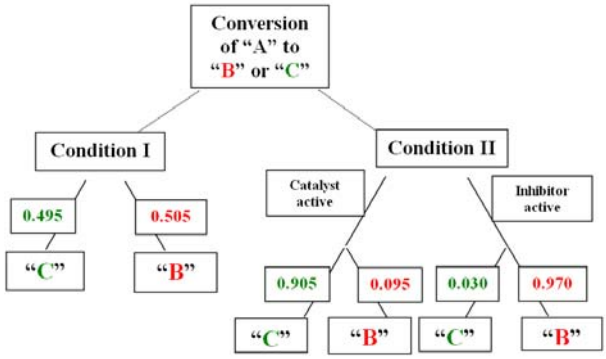
Table 1 describes some basic relationships between the game strategy that underlies Parrondo's paradox and this simple chemical model system.

Table 1. Relationships Between Parrondo's Paradox Strategies and a Model Chemical System

Parrondo's paradox game strategy	**Stochastic model of chemical system**
Games A/B	Conditions I/II
Winning outcome	Accumulation of product C
Losing outcome	Accumulation of product B
Probabilities	Relative reaction rates
ABABAB… switching	Conditions I/II – oscillating conditions (temperature, light/dark, pH etc.)
Games B1 vs B2	Condition II – catalyzed vs inhibited pathways
MOD2	Activity of "catalyst" vs "inhibitor"

An example of a reaction strategy that is analogous to a Parrondo's scheme is shown in Figure 2. In this case, Condition I is the alternate conversion of molecule A to products B or C following "probabilities" for each step analogous to relative reaction rates. In Condition I, the relative rate of formation of B is greater than that for the formation of C. Condition II has two arms in each of which A is converted to B or C. In condition II, the relative rates depend on the presence of a catalyst (formation of C is faster than B) or inhibitor (formation of B is faster than C). For Condition II alone, the overall rate of formation of B is greater than the rate of formation of C, i.e. "played" alone, B is the probable product. If the relative reaction rates are chosen properly (as they are in this example), then under oscillating conditions the formation of C under the catalytic arm of Condition II is sorted out and the rate of formation of C is greater by changing between Condition I and the catalytic arm of Condition II.

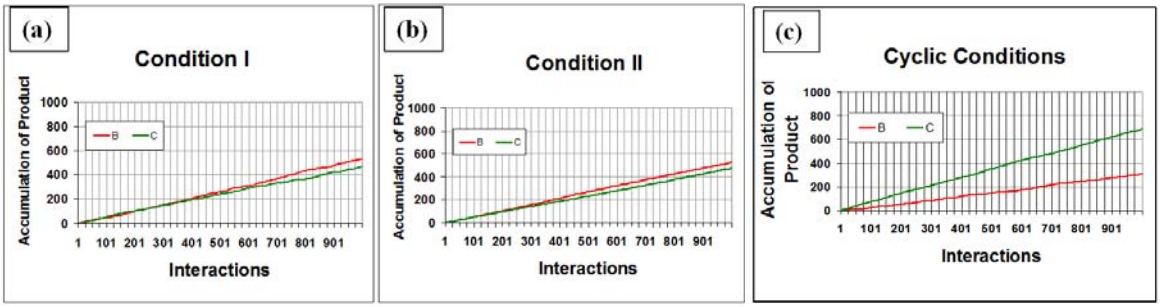
Figure 2. Typical Probabilities/Relative Rates for Conversion of "A" to "B" or "C" in the Stochastic Model of a Chemical System Displaying Parrondo's Paradox



A simple Excel program was created using the program's random number generator to calculate the accumulation of alternate products **B** and **C** from starting compound **A** and mimicking the game strategies of Parrondo's paradox. The program calculates the accumulation of products after 1000 iterations, i.e. reactive interactions converting molecule A to B or C. The model is a stochastic model because relative rates are calculated at each iteration based on probabilities

determined by a random number generator. Figure 4 shows the accumulation of B and C with Condition I alone, Condition II alone and oscillating conditions. In this model, more C accumulates under the oscillating conditions than under either steady state.

Figure 3. Accumulation of Products Predicted from the Stochastic Model: (a) Condition I alone; (b) Condition II alone; (c) Cycling between Conditions I and II



Deterministic chemical models of Parrondo's paradox

In the initial modlel, Conditions I and II could be various types of conditions. For the deterministic models temperature was used because kinetics are easy to model. This model was designed to displayed behavior reminiscent of Parrondo's paradox was based on a multi-step, feedback, autocatalytic system aided by a temperature-sensitive catalyst; the catalyst was active at a low temperature (Y) and inactive at high temperature (X). The chemical model is described by the following reactions. "A" and "B" are reactants and "C" is the target product:

A + B	**→ C**	**(uncatalyzed reaction)**
A + B + Y	**→ C + Y**	**(reaction catalyzed by Y)**
C	**→ 2 B**	**(C is a dimer of B)**
Y	**⇄ X**	**(the equilibrium between active form of the catalyst (Y) and inactive form of the catalyst(X))**

These reactions and their kinetic constants are input into the Kintecus 3.96 program. Kintecus is a powerful simulation program for chemical dynamics developed by James Ianni and is free for

academic use (31). As a deterministic, Arrhenius-based program the inputs include: the reaction steps, energies of activation, the Arrhenius constants, reactant concentrations and temperature profiles. The program assumes elementary reaction steps and solves numerically for the differential equations of the related rate laws. The concentrations of participating species are calculated and displayed over time at either a fixed temperature or under varying temperature conditions.

We describe here a typical set of conditions, the ABC Model, that highlight the paradoxical behavior that occurs under cycling temperature conditions. Initial concentrations are [A] = 1M (constant), [B] = $1x10^{-4}$M and [X] = $1x10^{-3}$M.

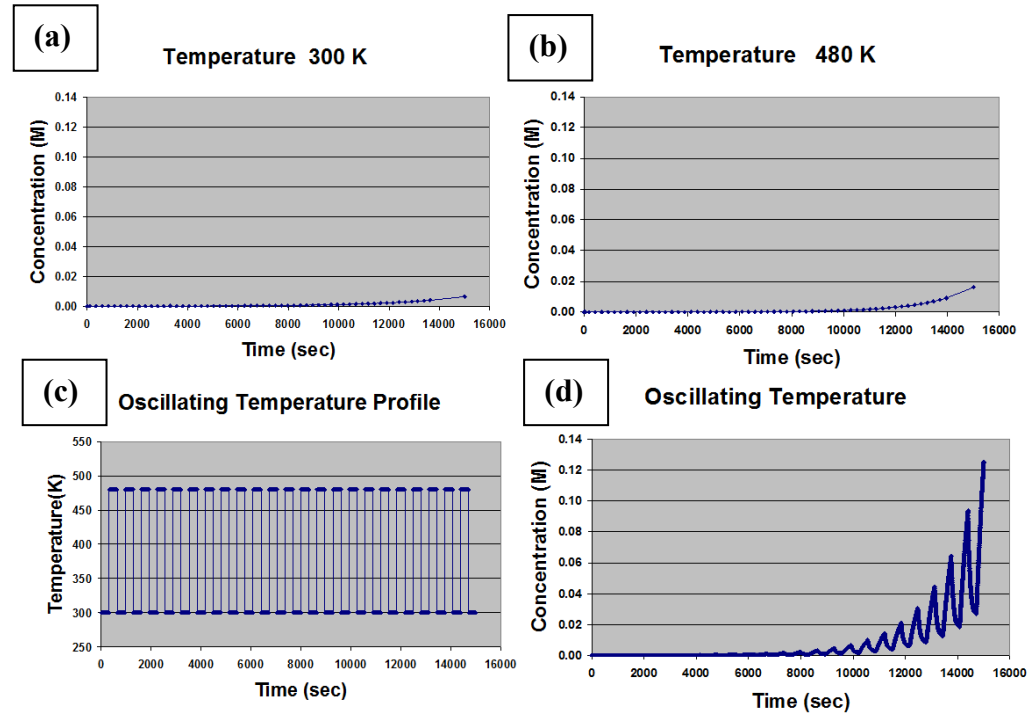
Figure 4 – The ABC Model - Input

#	Model Description SpreadSheet				k @ 300	k @480	
# A	T^m	Ea	Reaction	Comments	R	0.008315	kJ/mol K
1.00	0	7	X==>Y	k =	0.06043	0.1731	
100.00	0	12	Y==>X	A T^m e(-Ea/RT)	0.8141	4.945	
1.00	0	18	C ==> 2 B		7.345E-04	0.01100	
20.00	0	50	A + B ==> C		3.939E-08	7.25E-05	
20.00	0	1	A + B + Y ==> C + Y		13.39	15.57	

Figures 5a and 5b show the time course of the formation of C at fixed temperatures of 300K and 480K, respectively. Figure 6c shows the cycling temperature profile. The cycling temperature conditions drive oscillations of the concentrations of X and Y which in turn generates an asymmetrical oscillating increase in the concentration of C. The model predicts that at 300K, $6.5x10^{-3}$M C would be generated in 15,000 sec (Figure 5a) and at 480K, $1.6x10^{-2}$M C would be generated in the same time frame (Figure 5b). But, under oscillating temperatures (23 cycles in 15000sec), considerably more C is formed and 1.25 x 10^{-1}M C is generated (Figure 5d). More C

is produced under oscillating temperature conditions than under any steady state temperature between 300K and 480K. In the example we describe in Figure 5d, the concentration of C results from the square wave temperature profile (Figure 5c) which is easiest to analyze numerically (see next section). Similar results are obtained with a sinusoidal oscillating temperature profile.

Figure 5 – ABC Model: Synthesis of C at Steady State and Oscillating Temperature Conditions



Summary

Condition	Concentration of C at 15000 sec
300K	0.0065M
480K	0.016M
Oscillating Temperatures	0.125M

The paradoxical outcome of this model system was verified by examination of the differential equations that described the rate laws for the different steps of the reaction under different temperature profiles. The reactions

$$X \xrightarrow{k_1} Y: \quad Y \xrightarrow{k_2} X: \quad C \xrightarrow{k_3} 2B: \quad A+B+Y \xrightarrow{k_4} C+Y: \quad A+B \xrightarrow{k_5} C$$

may be modeled using the following kinematic reaction equations:

$$dX/dt = -k_1 X + k_2 Y: \qquad dY/dt = -k_2 Y + k_1 X$$
$$dB/dt = 2k_3 C - k_4 ABY - k_5 AB: \quad dC/dt = -k_3 C + k_4 ABY + k_5 AB$$
$$dA/dt = -k_4 ABY - k_5 AB$$

in which X represents the molar concentration of chemical X (initial value X_0), etc.,

the reaction constants $k_1,\ldots,k_5$ are obtained in the usual way using the Arrhenius equation:

$$\boldsymbol{k = A\ T^m\ e^{(-Ea/RT)}}$$

Where *A* is the Arrhenius constant, E_a is the energy of activation, R is the gas constant (0.008315 kJ/ mole K) and T is temperature in Kelvin; in the model systems, the temperature coefficient, m, is zero. Please distinguish between *A* the Arrhenius constant and A the reactant and its concentration. The X,Y equations are easily solved to yield:

$$Y(t) = [X_0(1 - e^{-(k_1+k_2)t}) + Y_0(1 + (k_2/k_1)e^{-(k_1+k_2)t})]/(1 + k_2/k_1)$$
$$X(t) = [X_0(k_2/k_1 + e^{-(k_1+k_2)t}) + (k_2/k_1)Y_0(1 - e^{-(k_1+k_2)t})]/(1 + k_2/k_1)$$

In chemical applications in which temperature is kept constant, k_1 and k_2 are usually such that X and Y very quickly "flatline," i.e. within seconds they acquire a constant value as it reachs equilibrium. Under this assumption, together with the assumption that the concentration of chemical A is constant, the A,B,C differential equations may also be solved to yield:

$$(\alpha_1 - \alpha_2)B(t) = B_0(\alpha_1 e^{-k_4'(1-\alpha_2)t} - \alpha_2 e^{-k_4'(1-\alpha_1)t}) + \alpha_1\alpha_2 C_0(e^{-k_4'(1-\alpha_2)t} - e^{-k_4'(1-\alpha_1)t})$$
$$(\alpha_1 - \alpha_2)C(t) = B_0(e^{-k_4'(1-\alpha_1)t} - e^{-k_4'(1-\alpha_2)t}) + C_0(\alpha_1 e^{-k_4'(1-\alpha_1)t} - \alpha_2 e^{-k_4'(1-\alpha_2)t})$$

in which the constants, α_1, α_2 are obtained using:

$$k_4' = k_4 A[(X_0+Y_0)/(1+k_2/k_1)] + k_5 A: \quad \eta = k_3/k_4': \quad 2\alpha_{1/2} = 1-\eta \pm \sqrt{(1-\eta)^2+8\eta}$$

The above limiting solutions of the reaction equations are found to fit the Kintecus numerical solution exactly. As calculated by the Kintecus program, the solutions correspondingly predict a significant increase in the production of C when the temperatures oscillate according to $T_1T_2T_1T_2$...

As noted, the temperature profile for the ABC Model cycles between 300K and 480K. No steady state temperature between 300K and 480K predicted more product C than thermal cycling. Also an excessively high temperature of 540K would be needed to generate as much product over the given time course as thermal cycling (Fig. 6). In addition, increasing the frequency of thermal cycling had a significant effect on increasing the overall rate of production of C. An examination of the changes in concentration of B and C under steady state and thermal cycling at the earliest times showed the exponential increase in C and the autocatalytic activity of B. Figure 7 shows that temperature switching increases the concentration of B over steady state temperature levels within the first thermal cycle; at the first instance of switching from 300K to 480K, there is a higher concentration of C than at 480K alone and this higher concentration of C drives the formation of B to a higher concentration under thermal cycling than at 480K alone. In addition, with thermal cycling the concentration of C begins to increase over steady state values after six cycles (not shown).

Figure 6. ABC Model: Formation of Product C at 15,000 sec under Different Steady State Temperature Conditions Compared to Thermal Cycling (dash line)

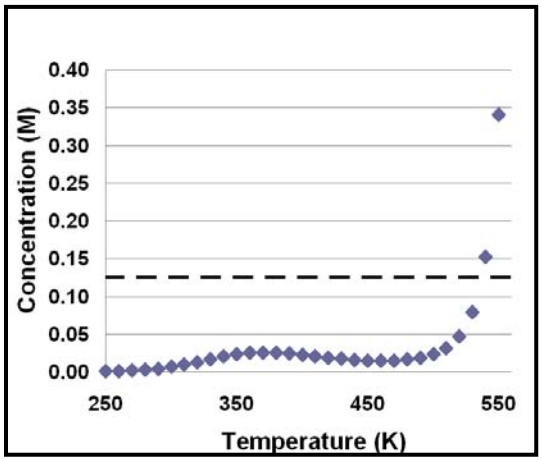
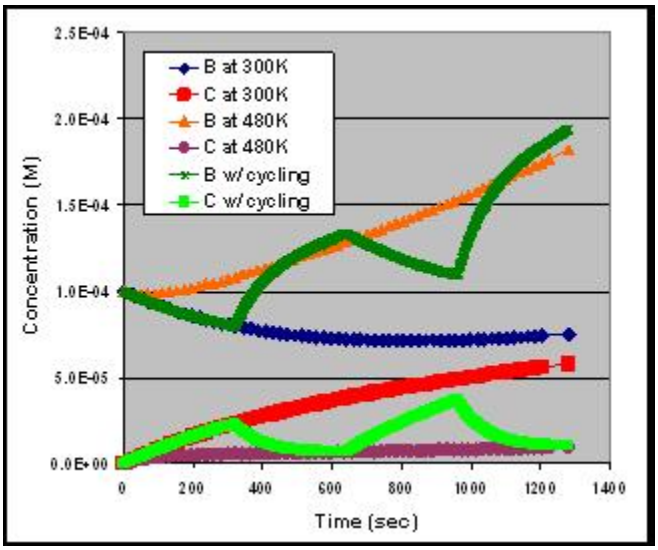


Figure 7. ABC Model: Predicted Concentrations of B and C at Earliest Times at 300K, 480K and with Temperature Cycling



Further verification of the behavior of this system under thermal oscillation was sought by examining the conditions for this model using the CKS program (not shown). This stochastically based program predicted the same results as generated by the Kintecus program.

The ABCD Model was designed to demonstrate the applicability of thermal cycling in another general chemical system in which the target product (D) did not participate in feedback and autocatalysis. The model (Fig. 8) and typical results (Fig. 9) are shown below. In this model we explored a shorter reaction time course (91 minutes) with a rapid temperature cycle. Product D is formed more rapidly under thermal cycling. The ABCD Model also predicts that, as expected, if [A] is not constant it becomes limiting for the formation of D over time (not shown).

Figure 8. ABCD Model: Input to Kintecus

# Model Description SpreadSheet				R =	0.0083145 kJ/mol K
# A	Ea	Reaction	Comments	k @ 300	k @480
1	2	X==>Y	k = A exp(-Ea/RT)	4.485E-01	6.058E-01
100	10	Y==>X		1.815E+00	8.162E+00
1	18	C ==> 2 B		7.345E-04	1.100E-02
20	50	A + B ==> C + D		3.940E-08	7.245E-05
20	1	A + B + Y ==> C + D + Y		1.339E+01	1.557E+01

Initial Concentrations

[A] = 1M (NB: not constant)
[X] = 1 x 10^{-3}M
[B] = 1 x 10^{-4}M

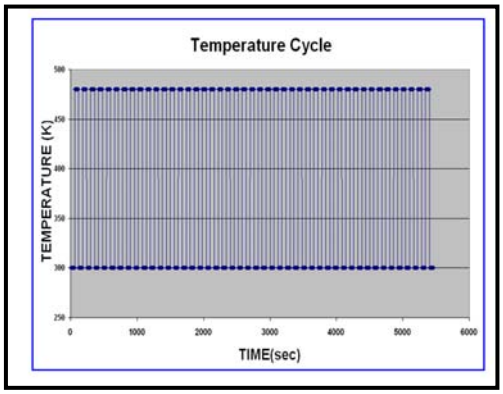
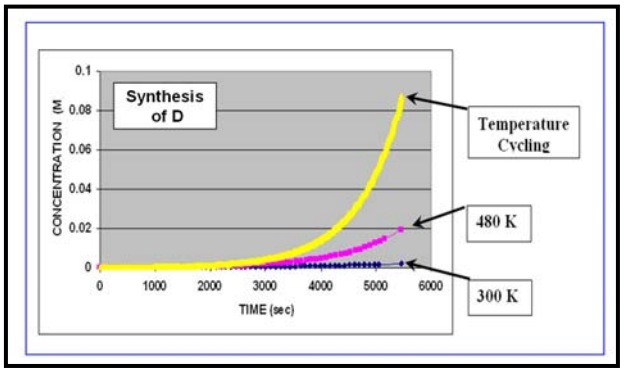


Figure 9. ABCD Model: Predicted Formation of D under Thermal Cycling and Steady State Temperatures and Summary Table of Results



Concentrations (Molar) after 5460 sec

	Thermal cycling	300K	480K
D	8.77 x 10^{-2}	2.20 x 10^{-3}	1.19 x 10^{-2}
B	4.87 x 10^{-2}	9.32 x 10^{-3}	1.61 x 10^{-2}
C	1.70 x 10^{-2}	4.34 x 10^{-4}	1.52 x 10^{-3}

Conclusions

A hallmark of systems chemistry is the fundamental realization that complex, behavior of even simple interacting reactions may not be easily reduced to understanding the activities of the individual constituents. Forced, external cycling conditions may cause interactions within chemical systems resulting in non-linear behavior that may be best explored with computational models. These models and their applications are likely to a critical aspect of the future of organic chemistry.

As of now, the vast majority of chemical reactions are conducted under fixed, constant conditions. Unlike spontaneous oscillating reactions, the models explored here describe systems carried out under thermal cycling conditions. Studies of thermal cycling include studies by J. Ross in biochemical systems found that forced oscillating changes in reactant concentrations created nonlinear behavior (15,16) and by R.D. Astumian et al. who demonstrated that cycling conditions can drive chemical systems far from equilibrium (17). Recently, a similar chemical model system was described in which thermal cycling accelerated reaction rates (18). J.M.R. Parrondo and colleagues reported that alternating between to two homogeneous systems can give rise to patterns and behaviors reminiscent of games based on Parrondo's paradox (7).

Real applications of thermal cycling in chemical systems are rare. Thermal cycling has been demonstrated to be important in using in enzyme-encapsulated hydrogel beads; changes in temperature change the bead volume reversibly bringing external reactant into the bead and forcing product out of the bead (20,21). Two-temperature PCR is a procedure that replicates DNA using thermal cycling (19). In chemical engineering, some microreactors have been designed in which oxidation of CO under fast forced oscillating temperatures has a faster reaction rate than under steady state but this paradoxical behavior has not been accompanied by an explanation of the underlying mechanism and extension to other chemical engineering systems has not yet materialized.

Our models suggest that, under the right conditions, exploring cycling conditions may be valuable in synthetic chemistry, bioorganic chemistry and chemical engineering. For example, thermal cycling may be particularly advantageous in template-directed organic chemistry (29) and devising more specific, efficient "one-pot" reaction systems with higher yields and better atom economy. In addition, our models suggest applications to breaking chiral symmetry; thermal cycling may be useful in devising new synthetic approaches and in developing new concepts related to prebiotic chemistry. Optimizing the variables in our initial models as well as developing new models will aid in understanding underlying interactions that will be important for extensions to actual applications.

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Reference

A. M. Turing, *Phil. Trans. of R. Soc. London* 1952, **B237**, 37.

V. Castets, E. Dulos, J. Boissonade and P. DeKepper, *Phys. Rev. Lett.*, 1990, **64**, 2953.

Q. Ouyang and H. L. Swinney, *Nature,* 1991, **352,** 610.

I. Lengyel and I. R. Epstein, *Proc. Natl. Acad. Sci. USA,* 1992,**89,** 3977.

J. M. R. Parrondo, in EEC HC&M Network on Complexity and Chaos (#ERBCHRX-

CT940546), ISI, Torino, Italy, 1996. Unpublished.

G. P. Harmer and D. Abbott, *Stat. Sci.* 1999,**14**, 206213.

G. P. Harmer and D. Abbott, *Nature,* 1999*,* **402**, 866.

Official Parrondo's pradox website www.eleceng.adelaide.edu.au/Groups/parrondo

T. K. Philips and A. B. Feldman, SSRN Abstract **2004** Available at: http://ssrn.com/abstract=581521.

A. P. Flitney and D. Abbott, *Physica A-Statistical Mechanics & its Applications,* 2003**, 324***,* 152.

J. M. R. Parrondo, G. P. Harmer and D. Abbott, *Phys. Rev. Lett.*, 2000**, 85**, 5226.

J. M. R. Parrondo and L. Dinis, *Contemporary Physics,* 2004*,* **45***,* 147.

H. Martin and H. C. von Baeyer, *American Journal of Physics,* 2004*,* **72***,* 710.

C. Barratt, *Transactions of ASME, J. of Vibns and Acoustics,*1997**, 119***,* 551.

J. C. Ianni, Kintecus , Windows Version 3.95, 2008, Available at: www.kintecus.com. and Kintecus Manual, available at: www.kintecus.com/Kintecus_V39.pdf

H. A. Hansen, J. L. Olsen, S. Jensen, O. Hansen, and U. J. Quaade, *Catalysis Communications*, 2006, **7**:272.

J. J. Brandner, G. Emig, M. A. Liauw and K. Schubert, *Chemical Engineering Journal*, 2004, **101**, 217.

J. J. Brandner, H. Hansen, O. Hansen, S. Jensen, L. Kiwi-Minsker, M. Luther, J. L. Olsen, U. J. Quaade, A. Renken and K. Schubert, ACHEMA 2006, Frankfurt am Main, Germany, 2006, paper 1284.

T. P. Lele, T. D. Pletcher and J. Lauterbach, J. *Am Inst. Chem. Eng. Journal,* 2001, **47**, 1418.

Z. Kang and Z. L. Wang, *Adv. Mater.*, 2003**, 15**, 521.

M. F. Kramer and D. M. Coen, *Current Protocols in Molecular Biology,* 2001**,** 15.1.1.

S. Mehra and W. S. Hu, *Biotechnology and Bioengineering*, 2005, **91**, 848.

E. Rubin and A. A. Levy, *Nucleic Acids Research*, 1996, ***24*****,** 3538.

J. Gevertz, S. Dunn and C. M. Roth, *Biotechnology and Bioengineering,* 2005**, 92**, 346.

J. T. Hsu, S. Das and S.C. Mohapatra, *Biotechnology and Bioengineering,* 1997, **55**, 359.

J. H. Horton, M. D. Hagen and M. S. Ko, *PCR Methods Appl.* 1994, **3***,* 359.

J. Buceta and K. Lindenberg, *Physical Review E*, 2002**, 66,** 046202-1.

J. Buceta, K. Lindenberg and J. M. R. Parrondo, *Physical Review Lett*, 2002**, 88**, 024103(1).

F. Diederich and P. J. Stang, (eds) Templated Organic Synthesis. Wiley-VCH: Weinheim. 1999**.**

P. Compain, V. Desvergnes, C. Ollivier, F. Robert, F. Suzenet, et al., *New J. Chem.*, 2006, **6**, 823.

R. F. Ludlow and S. Otto *Chem. Soc. Rev.***,** 2008**, 37,** 101**.**

M. Kindermann, I. Stahl, M. Reimold, W. M. Pankau and G. von Kiedrowski, *Angew Chem Int Ed Engl.,* 2005, **44**, 6750**.**

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