Nonlinear analysis of DNA breathing

Guillaume James

Université de Grenoble and CNRS, France

In collaboration with :

M. Peyrard, ENS Lyon and S. Cuesta-Lopez, Univ. Pol. Madrid

J. Cuevas and B. Sanchez-Rey, Univ. Sevilla

A. Levitt, univ. Paris-Dauphine and C. Ferreira, PUC-Rio

1 - Structure and « breathing » of DNA

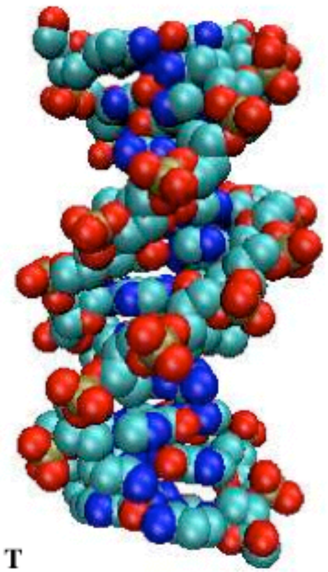
2 - Nonlinear model at the scale of base pairs

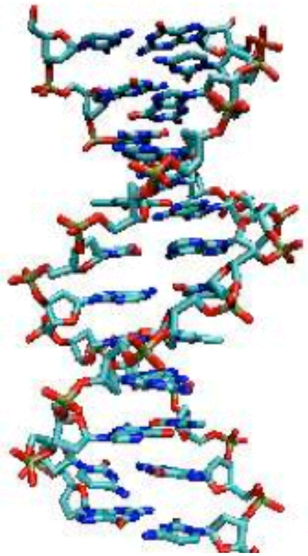
- ⇨Modification of the Peyrard-Bishop model
- ⇨DNA breathing = discrete breathers ?
- ⇨Comparison with experiments

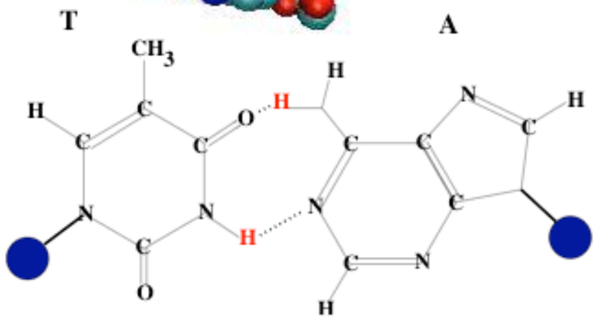
3 - Mathematical study of discrete breathers

- ⇨Numerical results
- ⇨Analysis of small amplitude breathers
- ⇨Analysis of large amplitude breathers

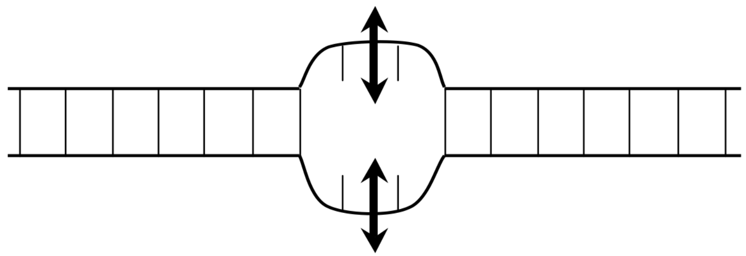
1- Structure and « breathing » of DNA







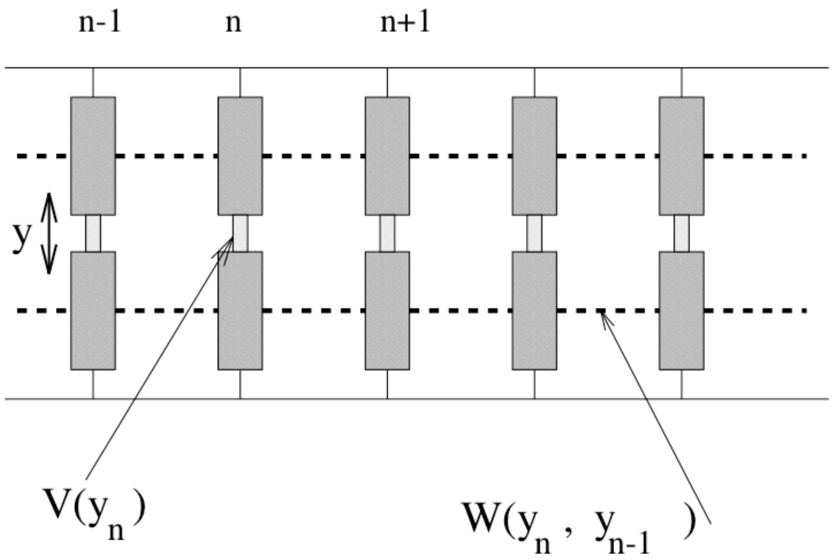
DNA base pair (AT)

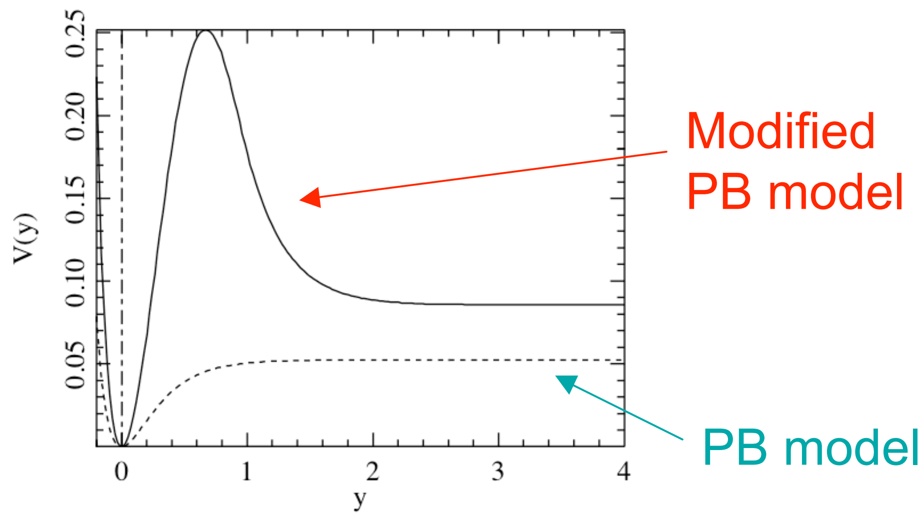


Hydrogen bonds relatively weak
⇨distance between the two bases fluctuates

DNA breathing :
spatially localized oscillations
detected in experiments

2 - Nonlinear model at the scale of DNA base pairs





✦ Peyrard-Bishop model : V = Morse potential
Peyrard-Bishop (89), Dauxois-Peyrard-Bishop (93)

✦ Modified PB model : V includes energy barrier for base pairs reclosing
Peyrard, Cuesta-Lopez and G.J., J. Biol. Phys. 35 (2009)

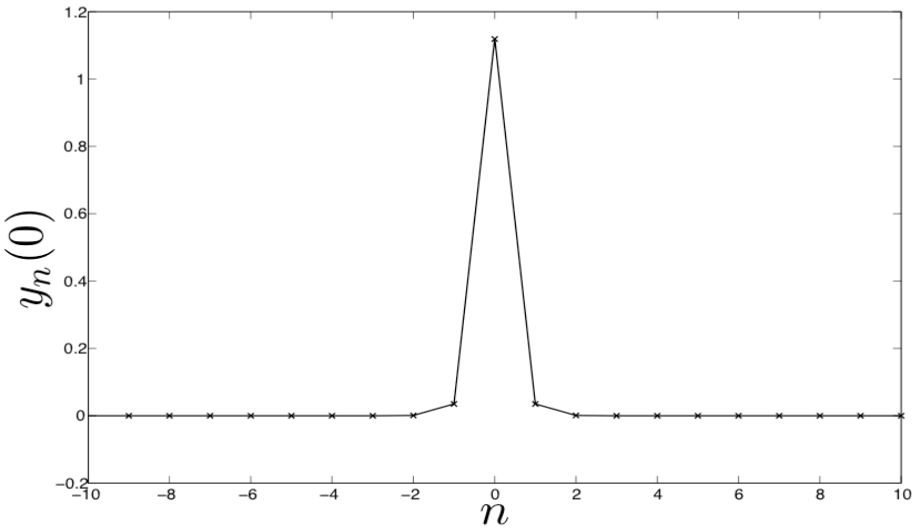
For open pairs : rotations hinder reclosing (missing d.o.f.), H bonds with water

Case with linear coupling :

$$W(y_n, y_{n-1}) = \frac{\gamma}{2}(y_n - y_{n-1})^2$$

$$\frac{d^2 y_n}{dt^2} + V'(y_n) = \gamma\,(y_{n+1} - 2y_n + y_{n-1})$$

Good candidates
to model DNA breathing :



Breathers ⇨

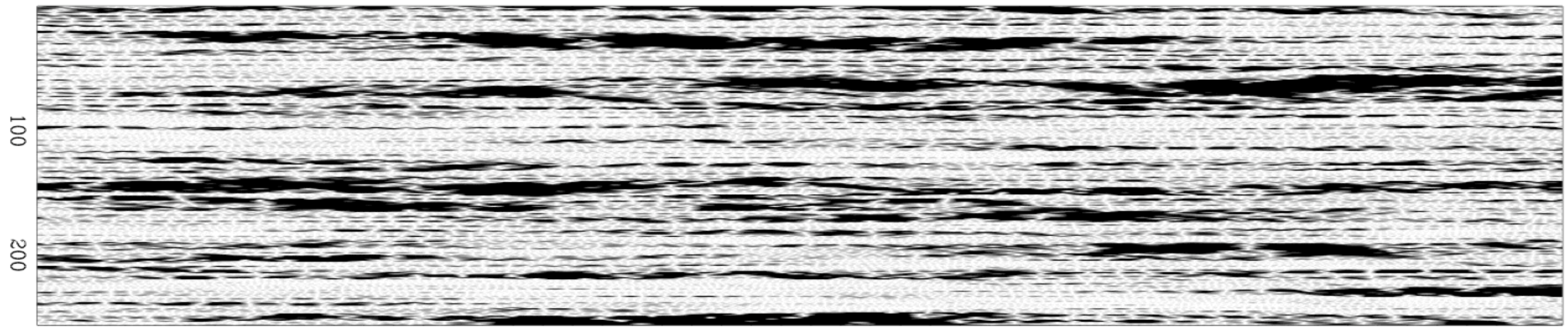
Breather : time-periodic, spatially localized solution

$$y_n(t+T) = y_n(t), \quad \lim_{n\to\pm\infty} y_n(t) = 0$$

$0 \leq t \leq 10^{-11} s$

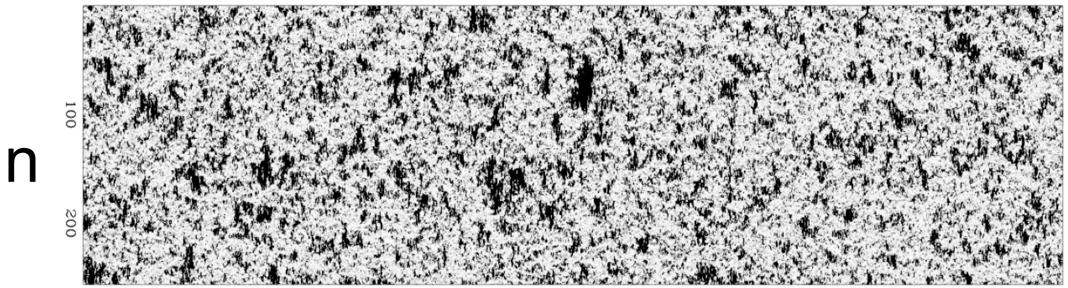
→

n



Peyrard-Bishop model (Morse potential) + Langevin thermostat :
grey level = stretching y_n of base pairs (black : $y_n \geq 2$ Å)

Barrier for reclosing ⇨better agreement with experiments !

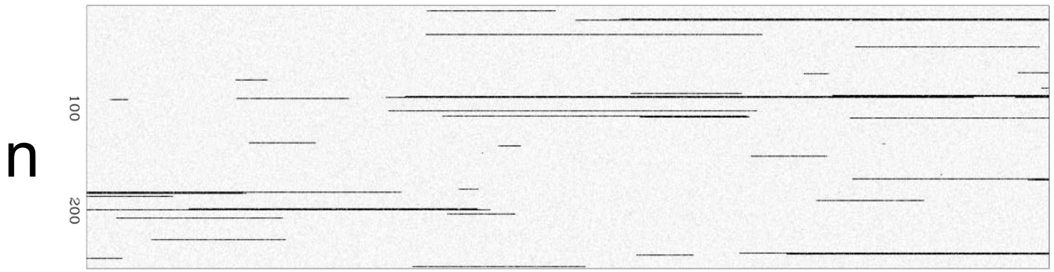


Thermal bath 270 K

Morse potential :

$$V(y) = A\left[e^{-\alpha y} - 1\right]^2$$

➔ $0 \leq t \leq 2.\ 10^{-8}$ s



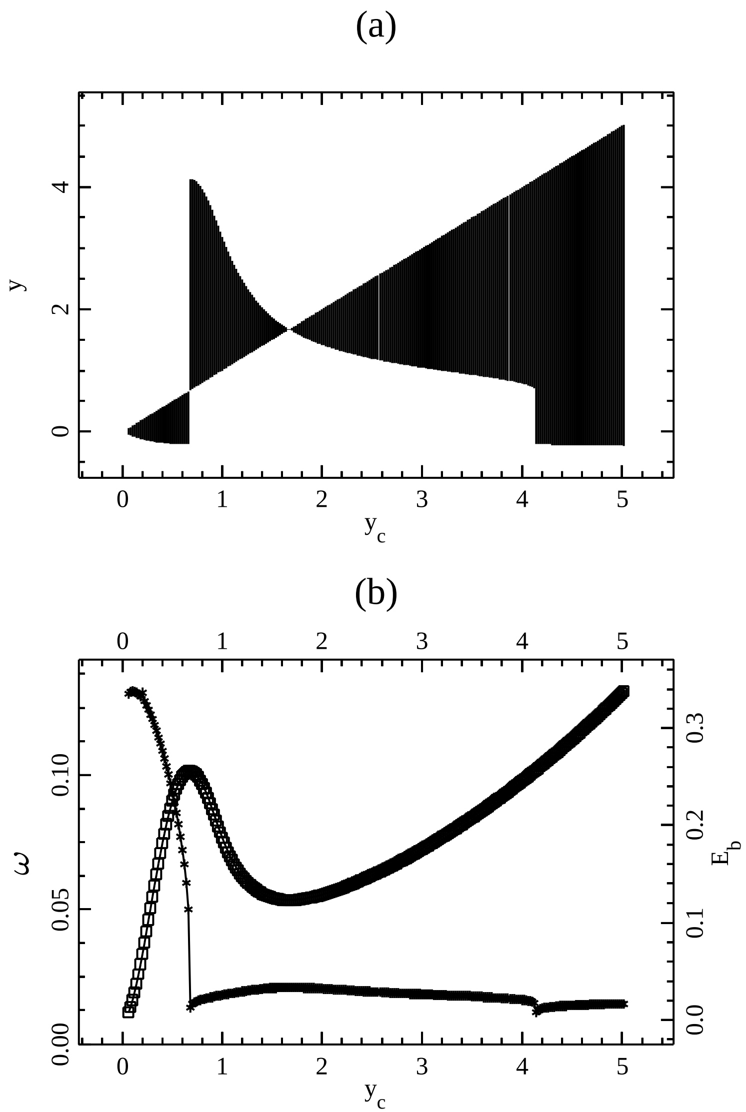
Potential with barrier for reclosing :

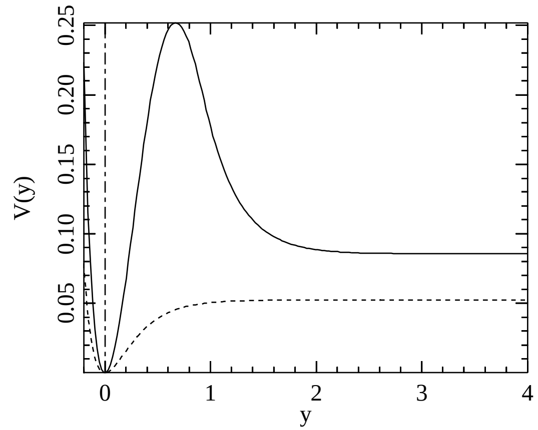
$$V(y) = \begin{cases} A\left[e^{-\alpha y} - 1\right]^2 & \text{if} \quad y < 0, \\ ay^2 + by^3 + cy^4 & \text{if} \quad 0 \leq y \leq 1, \\ D + Ee^{-\beta y}\left(y + \frac{1}{\beta}\right) & \text{if} \quad y > 1. \end{cases}$$

	Experiments	Morse	Barrier
Lifetime open	30-300 ns	0.08 ns	7 ns
Lifetime closed	1-10 ms	0.4 ns	0.4 µs

3- Mathematical study of discrete breathers :

Numerical results : relaxation towards a breather in the modified PB model





$\Longleftarrow$ Min and Max of $y_0(t)$ after transcient time

Initial condition : $y_n(0) = y_c\,\delta_{n,0}, \quad \dot{y}_n(0) = 0$

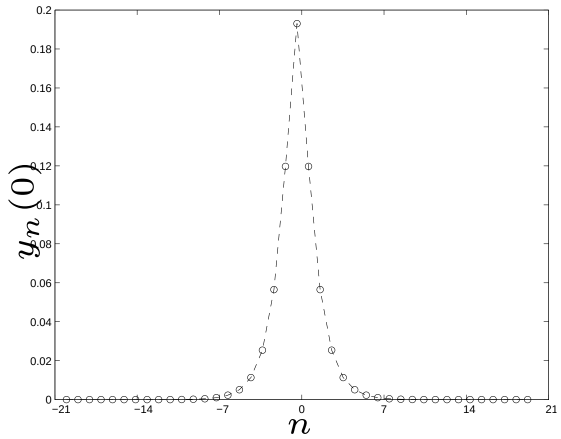
$\Longleftarrow$ Frequency ω and energy E_b of the asymptotic breather solution

(512 particles, absorbing boundary conditions, coupling $\gamma = 0.01$)

Existence theorems for discrete breathers in nonlinear lattices

$$y_n(t+T) = y_n(t)$$

$$\lim_{n\to\pm\infty} y_n(t) = 0 \quad \text{(infinite lattice)}$$



- **Small coupling γ :** MacKay, Aubry (94), Livi et al (97), Sepulchre, MacKay (97,98)

  G.J., Levitt, Ferreira (Appl. Analysis 89, 2010)

- **Variational methods :** Arioli et al (95-98), Aubry et al (01), Pankov (05)

- **Discrete spatial dynamics and center manifold reduction :** (small amplitude solutions)

  G.J. (01), G.J., Noble (04), Noble (04), G.J., Kastner (07), Georgi (08),

  G.J. (J. Nonlinear Sci. 13, 2003),

  G.J., Sánchez-Rey, Cuevas (Rev. Math. Phys. 21, 2009)

Small amplitude breathers via discrete spatial dynamics

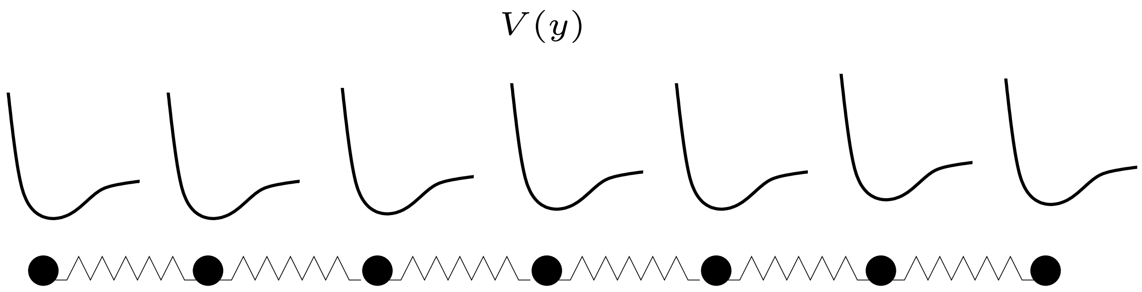
Klein-Gordon lattice :

$$\frac{d^2 y_n}{dt^2} + V'(y_n) = \gamma\,(\,y_{n+1} - 2\,y_n + y_{n-1}\,)$$

Linear coupling between nearest neighbors, $\gamma > 0$.

Anharmonic on-site potential V

$V'(0) = 0,\ V''(0) > 0.$



Time-periodic oscillations : $\tilde{y}_n(t+T) = \tilde{y}_n(t)$

$$\frac{d^2\tilde{y}_n}{dt^2} + \Omega^2\, V'(\tilde{y}_n) = \tilde{y}_{n+1} - 2\tilde{y}_n + \tilde{y}_{n-1}, \quad n \in \mathbb{Z}.$$

$V'(0) = 0$, $V''(0) = 1$

Rescale time : $y_n(\omega\, t) = \tilde{y}_n(t), \quad T = 2\pi/\omega$, $\quad y_n(t+2\pi) = y_n(t)$

Infinite-dimensional recurrence relation :

$$y_{n+1} = \omega^2\, \frac{d^2 y_n}{dt^2} + \Omega^2\, V'(y_n) + 2y_n - y_{n-1}, \quad n \in \mathbb{Z}$$

$y_n \in H^2$ for all $n \in \mathbb{Z}$

$H^2 = H^2(\mathbb{R}/2\pi\mathbb{Z})$ Sobolev space consisting of 2π-periodic functions of t

First order recurrence in a function space :

New variable $Y_n = (y_{n-1}, y_n) \in D$, $\quad D = H^2 \times H^2$

$$\forall n \in \mathbb{Z},\ \ Y_{n+1} = F_\omega(Y_n) \ \text{ in } \ X = H^2 \times L^2$$

$$F_\omega(y_{n-1}, y_n) = \left(y_n \, , \, \omega^2 \frac{d^2 y_n}{dt^2} + \Omega^2 V'(y_n) + 2y_n - y_{n-1} \right)$$

$F_\omega : D \longrightarrow X$ is C^k near $Y = 0$

Symmetries :

- $O(2)$ symmetry : F_ω commutes with $(T_\varphi Y)(t) = Y(t+\varphi)$, $\quad (S\,Y)(t) = Y(-t)$
- Reversibility : Y_n solution $\Rightarrow R\,Y_{-n}$ solution, $\quad R = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$

  originates from invariance $y_n(t) \longrightarrow y_{-n}(t)$

Spectral analysis :

Linearized operator at $Y = 0$: $\quad DF_\omega(0)(x, y) = \left(y\, ,\, (\omega^2 \frac{d^2}{dt^2} + \Omega^2 + 2)y - x \right)$

$DF_\omega(0) : D \subset X \to X$ closed, unbounded

Infinite number of double eigenvalues σ_k, σ_k^{-1} ($k \geq 0$) : $\quad \omega^2 k^2 = \Omega^2 + 2 - \sigma - \sigma^{-1}$

Reversibility $\Rightarrow$ invariance $\sigma \longrightarrow \sigma^{-1}$

$|\sigma_k| = 1 \Leftrightarrow$ resonances with linear waves (phonons) :

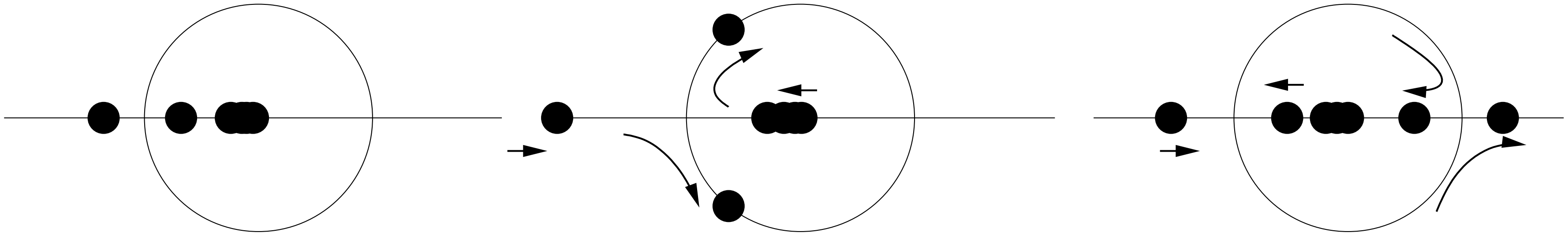
$$\tilde{y}_n(t) = A \cos\left(qn - \omega_q t + \varphi\right)$$

Dispersion relation : $\quad \omega_q^2 = \Omega^2 + 2(1 - \cos q)$

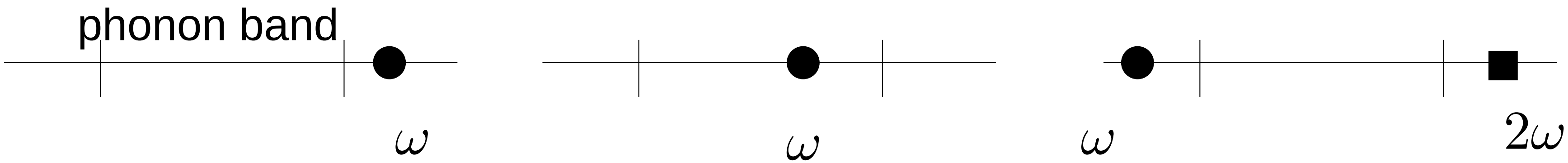
$\omega_q \in$ phonon band $[\Omega, (\Omega^2 + 4)^{1/2}]$

$k\, \omega = \omega_q \Leftrightarrow \sigma = e^{\pm iq}$ are double eigenvalues of $DF_\omega(0)$

Simplest bifurcations :



$\omega > (\Omega^2 + 4)^{1/2}$ $\qquad$ $\Omega < \omega < (\Omega^2 + 4)^{1/2}$ $\qquad$ $\frac{1}{2}(\Omega^2 + 4)^{1/2} < \omega < \Omega$



Part of the spectrum of $DF_\omega(0)$ near the unit circle. Case $\Omega > 2/\sqrt{3}$.

(unbounded spectrum on the real negative axis).

Local center manifolds for C^k maps :

$$u_{n+1} = F(u_n, \mu), \quad F : \mathbb{R}^N \times \mathbb{R}^p \to \mathbb{R}^N \text{ is } C^k, \quad F(0,0) = 0$$

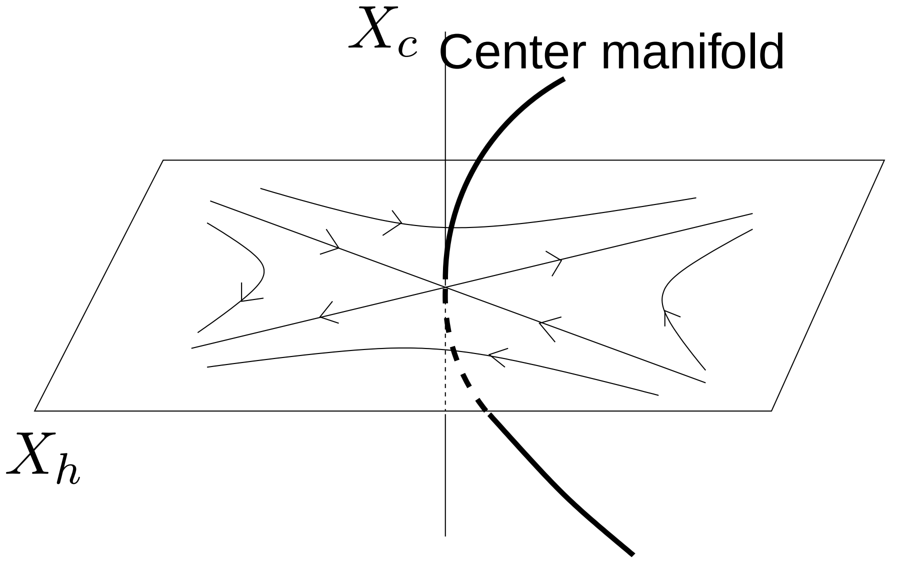
$$\mathbb{R}^N = X_c \oplus X_h \text{ invariant under } L = D_u F(0,0)$$

Local dynamics : $\quad u_{n+1} = L\, u_n, \quad \mathbf{u_{n+1}} = \mathbf{F}(\mathbf{u_n}, \mu)$

Eigenvalues σ_k :

$L_{|X_c} : |\sigma_k| = 1$

$L_{|X_h} : |\sigma_k| \neq 1$



More general case : $\quad E$ Banach space, $\quad F(., \mu) : E \to E$ is C^k

Marsden (76), Iooss (79)

Center manifolds for infinite-dimensional maps with an unbounded linear part :

$$\left.\begin{array}{r} \forall n \in \mathbb{Z}, \quad u_n \in D, \\ u_{n+1} = L\, u_n + N(u_n, \lambda) \quad \in X \end{array}\right\} \text{Hilbert spaces}$$

$L : D \subset X \to X$ closed unbounded linear operator

$N \;:\; D \times \mathbb{R}^p \to X$ is C^k $(k \geq 2)$

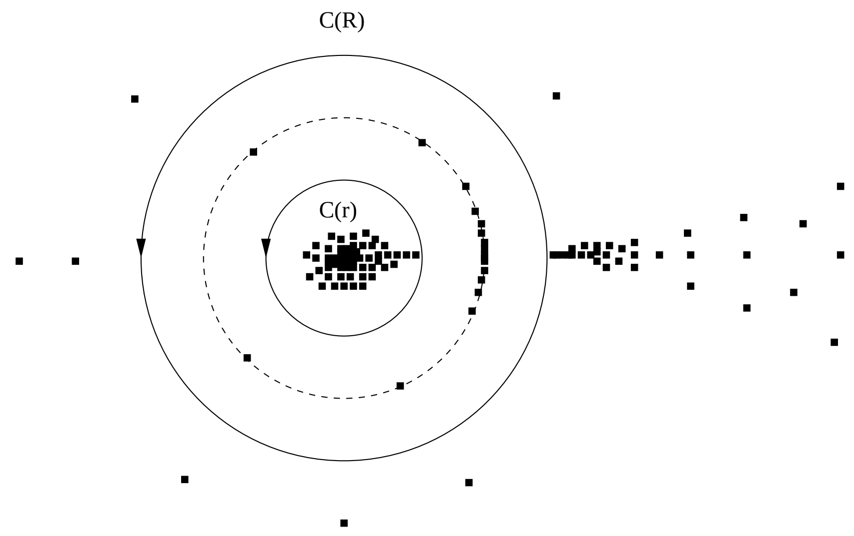
$N(u_n, \lambda)$ is $O(\, \|u_n\|_D^2 + \|\lambda\| \|u_n\|_D \,)$ as $(u_n, \lambda) \to 0$

Small parameter : $\lambda \in \mathbb{R}^p$

Center manifold reduction theorem : G.J., J. Nonlinear Sci. (2003)

SPECTRUM OF L :

$$\sigma(L) = \sigma_s \cup \sigma_c \cup \sigma_u,$$



SPECTRAL SEPARATION : $\sup_{z \in \sigma_s} |z| < 1, \quad |z| = 1 \ \forall z \in \sigma_c, \quad \inf_{z \in \sigma_u} |z| > 1$

Central subspace not necessarily finite-dimensional.

Spectral projection : $\pi_c = \dfrac{1}{2i\pi} \displaystyle\int_{\mathcal{C}(R)} (zI - L)^{-1} \, dz - \dfrac{1}{2i\pi} \displaystyle\int_{\mathcal{C}(r)} (zI - L)^{-1} \, dz$

$X_c = \pi_c X \subset D$, $\quad X = X_c \oplus X_h, \quad D = X_c \oplus D_h$

$$u_{n+1} = L\, u_n + N(u_n, \lambda)$$

CENTER MANIFOLD THEOREM : Assume spectral separation for L

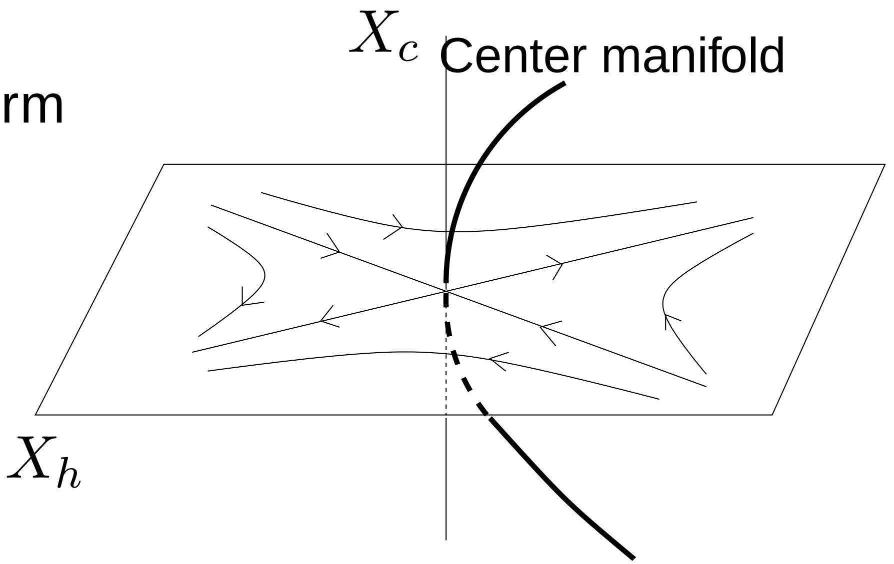
For $\lambda \approx 0$:

- orbits staying close to 0 in D lie on a C^k local center manifold $\mathcal{M}_\lambda \subset D$,
- $\mathcal{M}_\lambda$ is locally invariant under $L + N(., \lambda)$,
- $\mathcal{M}_\lambda$ is locally a graph on X_c, tangent to X_c at $u = 0$ for $\lambda = 0$.

Small amplitude solutions have the form

$$u_n = u_n^c + u_n^h$$

$$u_n^h = \psi(u_n^c, \lambda)$$



Application to Klein-Gordon lattices :

G.J., Sanchez-Rey, Cuevas, Rev. Math. Phys. (2009)

$$\omega^2 \frac{d^2 y_n}{dt^2} + \Omega^2 V'(y_n) = y_{n+1} - 2y_n + y_{n-1}$$

Consider $\omega_c > 0$ with

$$p\,\omega_c \in [\Omega, (4+\Omega^2)^{1/2}] \text{ for all } p \in \{p_0, \ldots, p_1\}$$

with no additional multiples in this interval.

Number of resonant modes : $N = p_1 - p_0 + 1$.

$\Rightarrow$ apply the center manifold theorem with $\lambda = \omega - \omega_c \approx 0$

dim $X_c = 4N$, $\quad X_c = H_c \times H_c$

$H_c =$ Span $\{ \cos(p_0 t), \sin(p_0 t), \ldots, \cos(p_1 t), \sin(p_1 t) \}$

$H^2 = H_c \oplus H_h$

REDUCTION THEOREM :

For $\omega \approx \omega_c$, all solutions y_n staying close to 0 in H^2 for all $n \in \mathbb{Z}$ satisfy

$$
\begin{aligned}
y_n(t) \;\; = \;\; & \sum_{p=p_0}^{p_1} \left[\, \beta_n^{(p)} \, \cos{(pt)} + \gamma_n^{(p)} \, \sin{(pt)} \,\right] \\
& + \phi(\, \beta_{n-1}^{(p_0)}, \gamma_{n-1}^{(p_0)}, \beta_n^{(p_0)}, \gamma_n^{(p_0)}, \ldots, \beta_{n-1}^{(p_1)}, \gamma_{n-1}^{(p_1)}, \beta_n^{(p_1)}, \gamma_n^{(p_1)}, \omega \,)(t)
\end{aligned}
$$

$\phi \,:\, \mathbb{R}^{4N} \times \mathbb{R} \longrightarrow H_h$ is C^k near $(0, \omega_c)$

$\phi(0,\omega) = 0$, $D\phi(0,\omega_c) = 0$

$\Rightarrow$ infinite-dimensional problem locally reduced to a finite-dimensional mapping for

$$
(\, \beta_{n-1}^{(p_0)}, \gamma_{n-1}^{(p_0)}, \beta_n^{(p_0)}, \gamma_n^{(p_0)}, \ldots, \beta_{n-1}^{(p_1)}, \gamma_{n-1}^{(p_1)}, \beta_n^{(p_1)}, \gamma_n^{(p_1)} \,) \;\in\; \mathbb{R}^{4N}
$$

Reduction not restricted to localized oscillations

Study of the reduced recurrence relation :

Solutions even in time, case $\omega \approx \Omega$ and $\Omega > 2/\sqrt{3}$ $(N = 1)$

$$\beta_{n+1} - 2\beta_n + \beta_{n-1} = (\Omega^2 - \omega^2)\,\beta_n + B\,\beta_n^3 + \text{ h.o.t.}$$

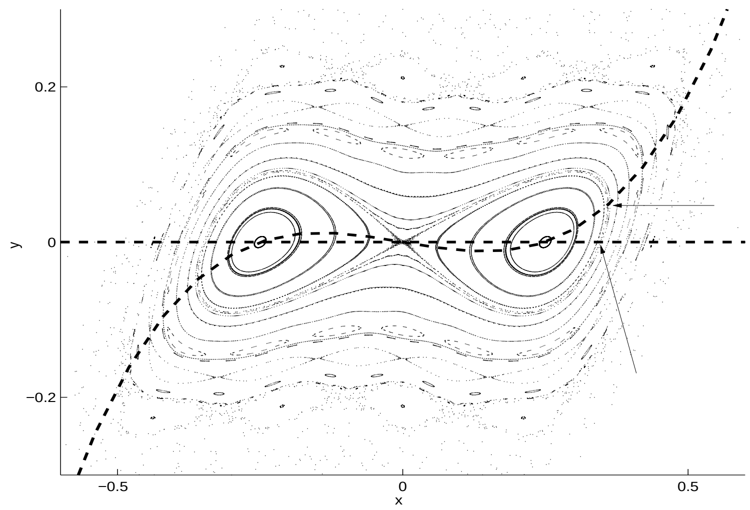
$$B = \frac{\Omega^2}{8}\left(V^{(4)}(0) - \frac{5}{3}(V^{(3)}(0))^2 \right)$$

Reversible mapping :

$$X_{n+1} = G_\omega(X_n),$$

$$X_n = (\beta_n, \beta_n - \beta_{n-1}).$$

Orbits of the map for $\omega < \Omega$, $\omega \approx \Omega$ and $B < 0$ (soft potential V) :



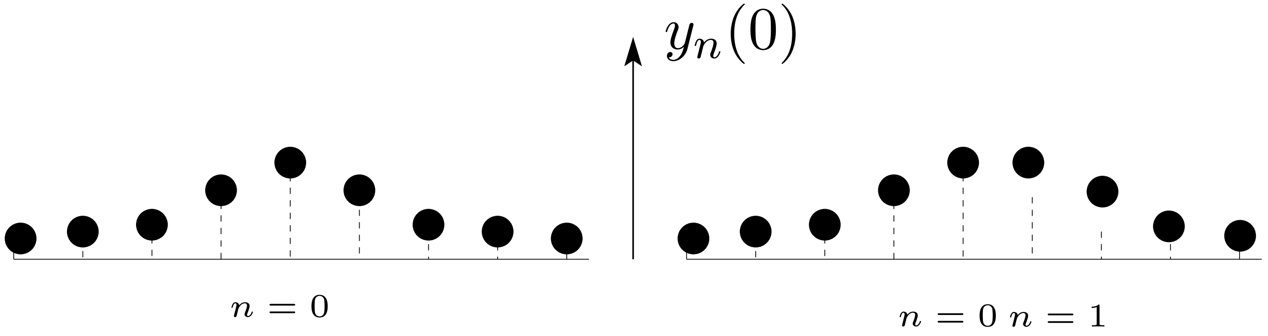
$$(G_\omega R_i)^2 = I, \quad \text{symmetry } R_1\,(x, y) = (x - y, -y), \quad \text{involution } R_2 = R_1\,G_\omega$$

Dashed curves : fixed points of R_1 (axis $y = 0$) and R_2.

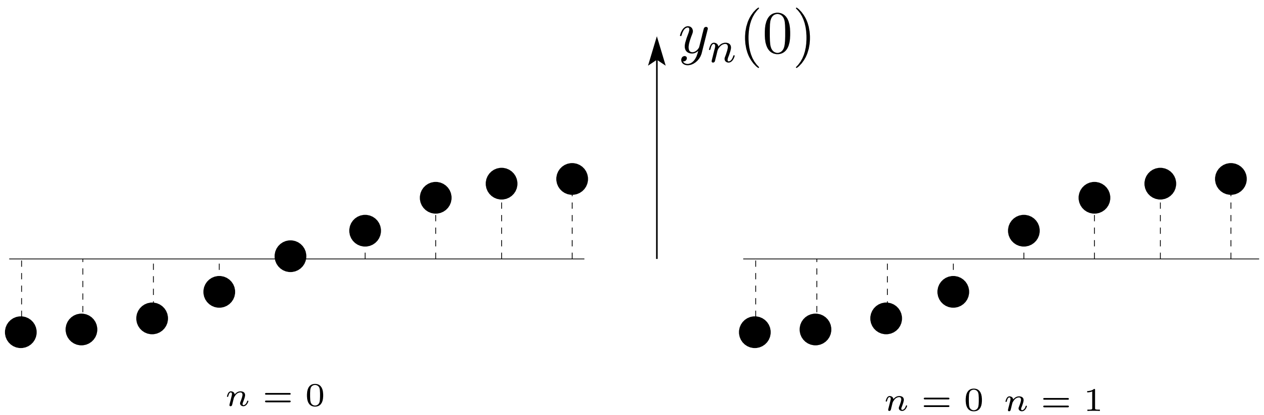
Reversible orbits homoclinic to 0 : $R_1 X^1_{-n+2} = X^1_n$, $R_2 X^2_{-n} = X^2_n$

THEOREM (small amplitude breathers in Klein-Gordon lattices)

There exist localized solutions (breathers) for $B < 0$, or fronts (dark solitons) for $B > 0$, $\frac{2\pi}{\omega}$-periodic in t, having a small amplitude for $\omega \approx \Omega$



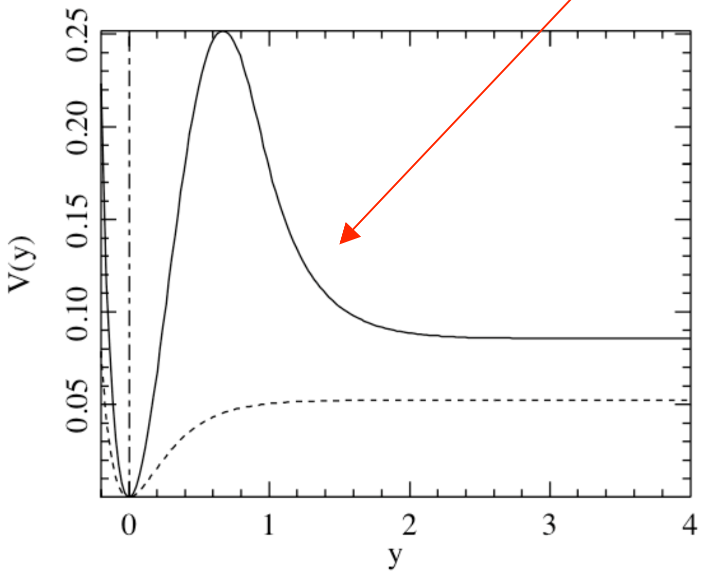
breather centered at $n = 0$ breather centered at $n = 1/2$



dark soliton centered at $n = 0$ dark soliton centered at $n = 1/2$

Large amplitude breathers : continuation from infinity

Modified
PB model



Potential with barrier
for reclosing :

$$V(y) = \begin{cases} A\left[e^{-\alpha y} - 1\right]^2 & \text{if} \quad y < 0, \\ ay^2 + by^3 + cy^4 & \text{if} \quad 0 \le y \le 1, \\ D + Ee^{-\beta y}\left(y + \frac{1}{\beta}\right) & \text{if} \quad y > 1. \end{cases}$$

Peyrard, Cuesta-Lopez and G.J. (2009); G.J., Levitt and Ferreira (2010)

Approximate description of single-site breathers (n=0) :

⇨Component n=0 of dynamical equations :

$$\frac{d^2 y_0}{dt^2} + V'_\gamma(y_0) = \gamma\,(y_1 + y_{-1}).$$

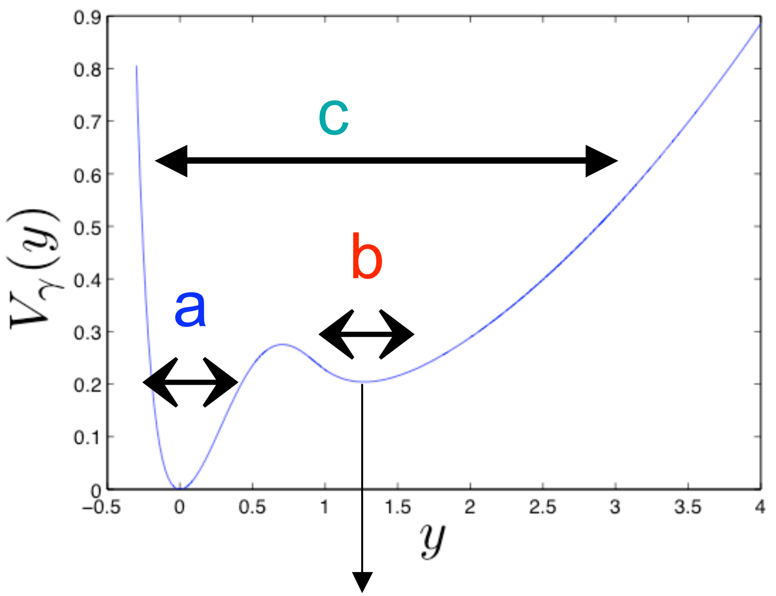
$$V_\gamma(y) = V(y) + \gamma y^2$$

⇨Approximate problem :

$$y_1 = y_{-1} = 0 \qquad \frac{d^2 y_0}{dt^2} + V'_\gamma(y_0) = 0.$$

Single-site approximation :

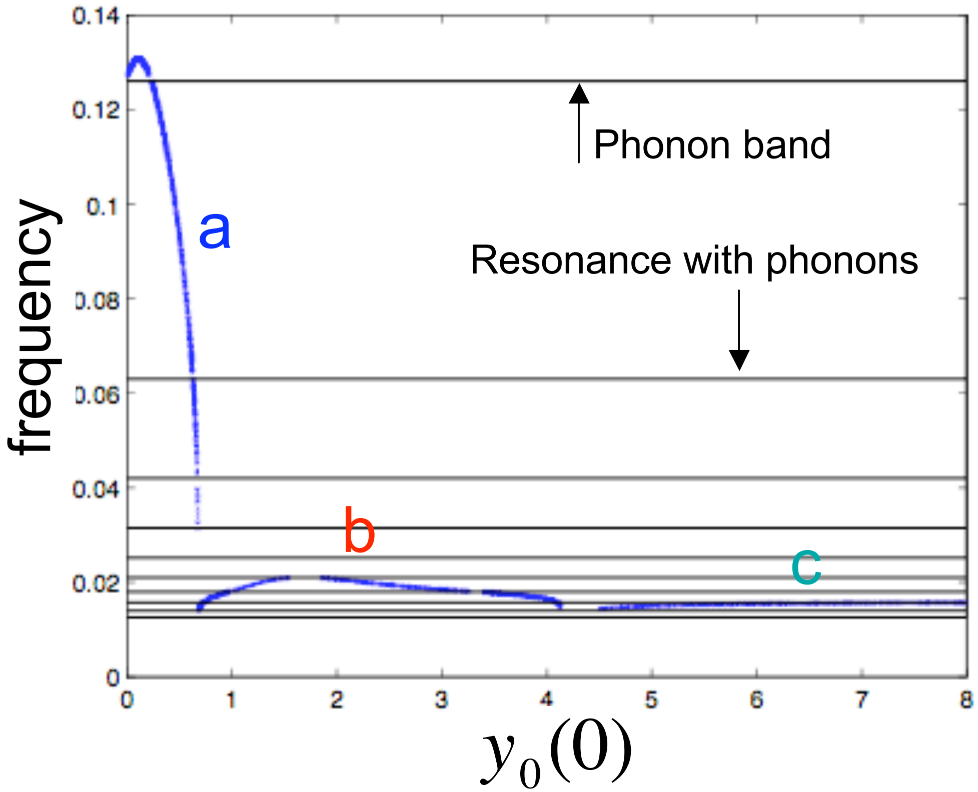
$$\frac{d^2 y_0}{dt^2} + V_\gamma'(y_0) = 0.$$



Local min $\tilde{y}_0 = -\frac{1}{\beta}\ln\left(\frac{2\gamma}{\beta E}\right)$

Numerical computation (40 sites)

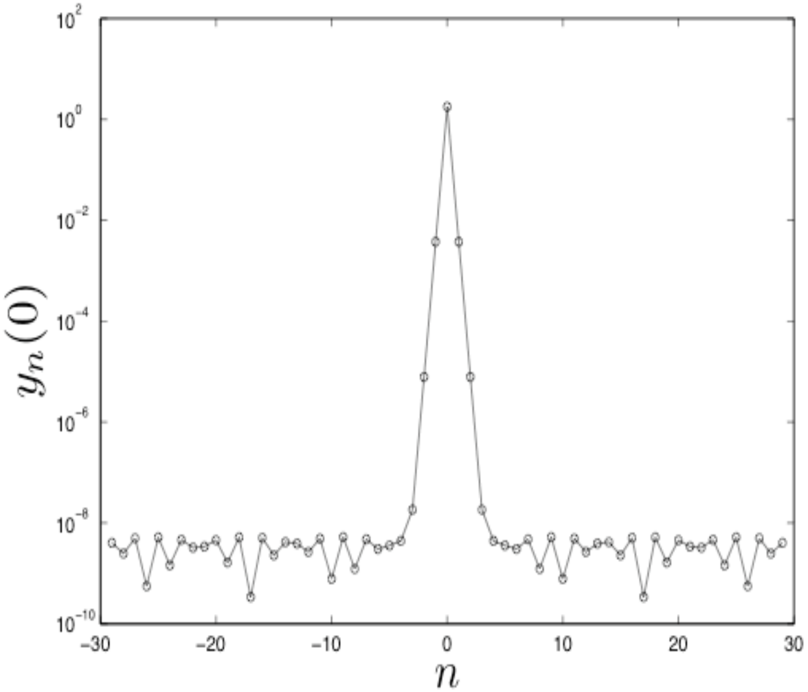
Gauss-Newton algorithm, path following



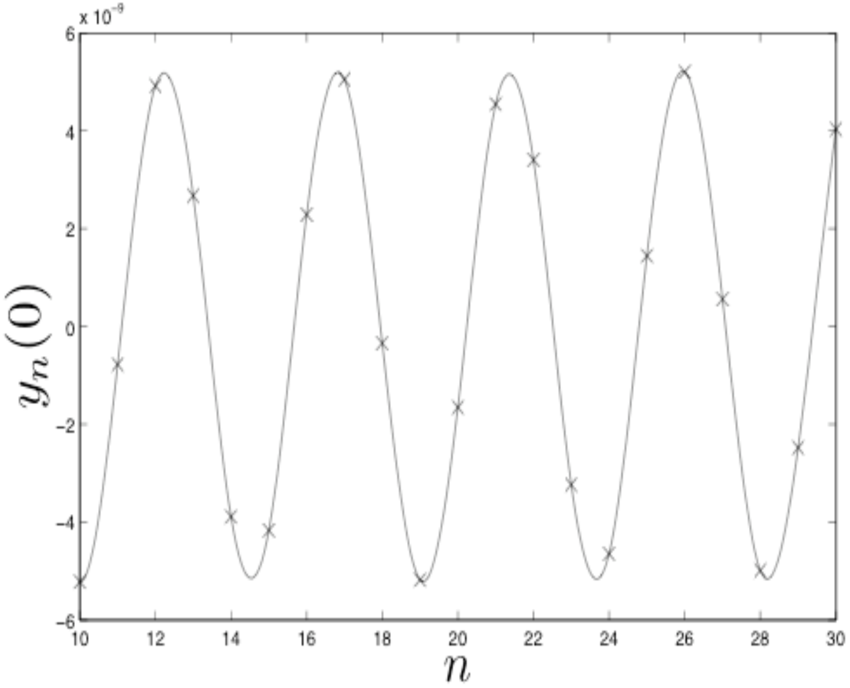
When coupling γ→0, amplitudes of breathers b, c →∞

Breather in resonance with a phonon :

« phonobreather » (Morgante, Johansson, Aubry, Kopidakis, 02)



Spatial profile (logarithmic scale)



Zoom on the oscillatory tail

Existence of breathers beyond the barrier by continuation from infinity

G.J., Levitt and Ferreira, Appl. Analysis 89 (2010)

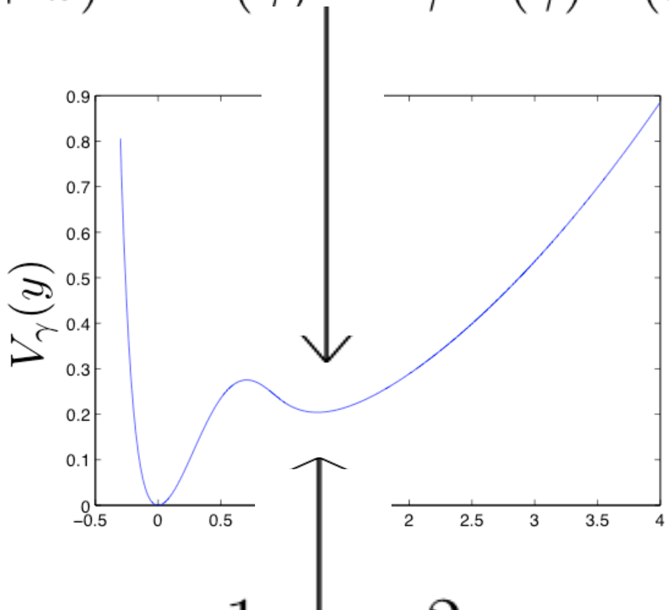
1- construction of an approximate solution y_n^* for small γ

2- contraction mapping thm ⇒ exact solution close to y_n^*

Classical anticontinuum limit (MacKay, Aubry 94) cannot be used

$$V_\gamma(\tilde{y}_0 + \tilde{x}) = \tilde{D}(\gamma) - 2\gamma \ln(\gamma)\, \Phi(\tilde{x}) + 2\gamma\, U(\tilde{x})$$

$$\Phi(x) = \frac{1}{\beta^2}(e^{-\beta x} - 1 + \beta x)$$



$$\tilde{y}_0 = -\frac{1}{\beta} \ln\left(\frac{2\gamma}{\beta E}\right)$$

Approximate breather solution :

$$y_n^*(t) = \delta_{n,0}\left[-\frac{1}{\beta} \ln\left(\frac{2\gamma}{\beta E}\right) + x\left(\sqrt{-2\gamma \ln(\gamma)}\, t\right)\right]$$

$$\frac{d^2 x}{dt^2} + \Phi'(x) = 0$$

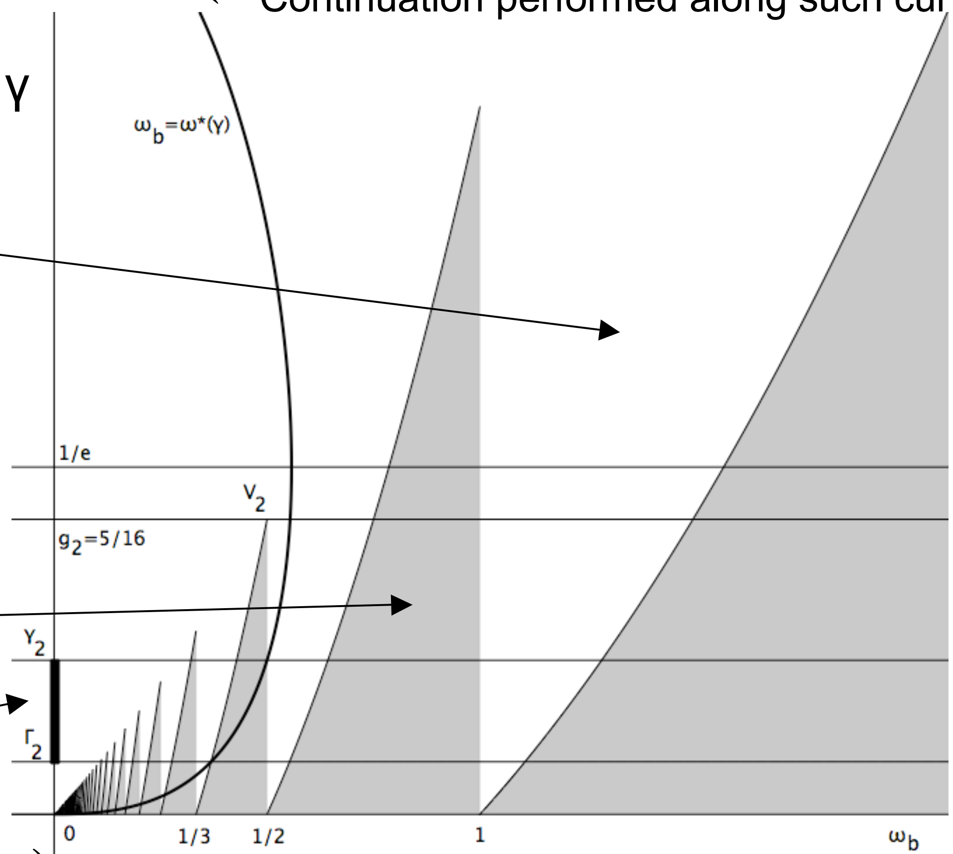
x periodic, frequency ω

Continuation / γ :   γ→0, variable breather frequency $\omega^*(\gamma) = \omega\sqrt{-2\gamma\ln(\gamma)}$

➪resonances with normal modes $y_n(t) = A\cos(qn - \omega_q t)$
prevent continuation in a connected neighborhood of γ=0

← Continuation performed along such curves

Coupling γ



Breather frequency

White region : phonon band
$$\omega_q^2 = 1 + 2\gamma(1 - \cos q)$$
and submultiples

Grey region :
nonresonance bands

Nonresonance for
$$\gamma \in \cup_{m \geq m_0(\omega)} (\Gamma_m, \gamma_m) = NR(\omega)$$

(infinite union of disjoint intervals accumulating near γ=0)

Theorem :

Consider a periodic solution t→x(t) (even in t) of : $\dfrac{d^2x}{dt^2} + \Phi'(x) = 0$
(frequency ω=2π/T) and the associated approximate breather y_n^*

For all small enough $\gamma \in \cup_{m\geq p}[\,\tilde{\Gamma}_m, \tilde{\gamma}_m\,] \subset NR(\omega)$
(subset of $NR(\omega)$ of asympt. full relative Lebesgue meas. as γ→0),
there exists a breather solution of :

$$\frac{d^2 y_n}{dt^2} + V'(y_n) = \gamma\,(y_{n+1} - 2y_n + y_{n-1}), \quad n \in \mathbb{Z},$$

close to the approximate solution y_n^* , i.e. having the form

$$y_n(t) = y_n^*(t) + \xi_n(\sqrt{-2\gamma\ln(\gamma)}\,t),$$

$$\|\xi_0\|_{H^2(0,T)} = O(|\ln\gamma|^{-1}) \qquad\qquad \|\xi_n\|_{H^2(0,T)} = o(\gamma^{|n|/2}) \ \text{ for } \ n \neq 0$$

The map $\gamma \mapsto (\xi_n)_{n\in\mathbb{Z}}$ is C^k from $\cup_{m\geq p}[\,\tilde{\Gamma}_m, \tilde{\gamma}_m\,]$ to $\ell_\infty(\mathbb{Z}, H_e^2(0,T))$

Conclusion

- ❖ Modification of the Peyrard-Bishop model for DNA breathing:

Energy barrier for base pair reclosing ⇨ better agreement with experiments, but average lifetime of closed state much smaller / experiments

Existence of a new kind of breather oscillating around a localized equilibrium

- ❖ Existence of discrete breathers by continuation from infinity :

New analytical technique valid at small coupling

Extensions : resonant breathers with an oscillatory tail, breathers oscillating in the two potential wells (G.J. and Pelinovsky, in preparation)

- ❖ Future challenges : sequence effects, estimate of transition times (open/closed) in the presence of noise, accurate modelling of thermal noise