# Optimization of Perron eigenvectors and applications: from web ranking to chronotherapeutics

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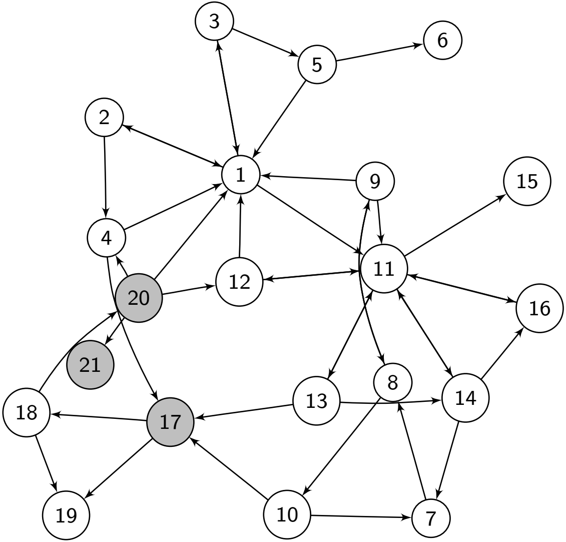
# Outline

# Web ranking

A webmaster controls a given number of pages:

- May add links
- Must respect the content
  (the goal of a site is to provide information or service)
- Wishes to maximize:
  - Income (number of clicks on ads, number of sales)
  - Visibility (Sum of PageRank values of the site, PageRank of home page in Google)

# Toy example with 21 pages




Nodes = web pages

Arcs = hyperlinks

(21) : controlled page

(1) : non controlled page

# Definition of PageRank [Brin and Page, 1998]

- Random web surfer moves from page $i$ to page $j$ with probability $\frac{1}{D_i}$ ($D_i =$ degree of page $i$)
- $\pi =$ invariant measure of the Markov chain

$$\pi_i = \sum_{j : j \to i} \frac{\pi_j}{D_j}$$

- An important page is a page linked to by important pages
- Markov chain model may be reducible

# Definition of PageRank [Brin and Page, 1998]

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- $\pi$ = invariant measure of the Markov chain

$$\pi_i = \alpha \sum_{j:j\to i} \frac{\pi_j}{D_j} + (1-\alpha) z_i$$

- An important page is a page linked to by important pages
- Markov chain model may be reducible
  $\rightarrow$ with probability $1-\alpha$, surfer gets bored and resets: new research from page $i$ with probability $z_i$
- Transition matrix: $P_{i,j} > 0, \forall i, j$ (usually $\alpha = 0.85$)
- PageRank is the unique invariant measure $\pi$ of $P$

# The PageRank optimization problem

- Well studied subject: Avratchenkov and Litvak, 2006
  Mathieu and Viennot 2006
  De Kerchove, Ninove and Van Dooren 2008
  Csáji, Jungers and Blondel 2010...
- Obligatory links $\mathcal{O}$, facultative links $\mathcal{F}$, prohibited links $\mathcal{I}$ (Strategy set proposed by Ishii and Tempo, 2010)
- Utility $\varphi(\pi, P) = \sum_i r_{i,j} \pi_i P_{i,j}$
- $r_{i,j}$ is viewed as reward by click on $i \to j$
- [Fercoq, Akian, Bouhtou, Gaubert, to appear in IEEE TAC]

# Reduction to ergodic control

## Proposition

*$\mathcal{P}_i$ = set of admissible transition probabilities from Page $i$*

*The PageRank Optimization problem is equivalent to the ergodic control problem with process $X_t$:*

$$\max_{(\nu_t)_{t\geq 0}} \liminf_{T\to+\infty} \frac{1}{T}\mathbb{E}(\sum_{t=0}^{T-1} r_{X_t,X_{t+1}})$$

$$\nu_t \in \mathcal{P}_{X_t}, \forall t \geq 0$$

$$\mathbb{P}(X_{t+1} = j | X_t = i, \nu_t = p) = p_j, \forall i, j \in [n], \forall p \in \mathcal{P}_i, \forall t \geq 0$$

*where $\nu_t$ is a function of the history $(X_0, \nu_0, \ldots, X_{t-1}, \nu_{t-1}, X_t)$*

# Exponential size of the action sets

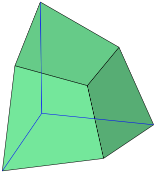
- At each page $i$, an action corresponds equivalently to
  - select $J \subseteq \mathcal{F}_i$
  - select $\nu \in \mathcal{P}_i$, a uniform measure on $J$
- $2^n$ hyperlink configurations by controlled page
- Classical Markov Decision Process techniques fail
- Csáji, Jungers and Blondel, 2010: graph rewriting to optimize the rank of a single page
- Our solution: action sets have a concise description

# Admissible transition probabilities

## Theorem

*The convex hull of the set of admissible transition probabilities is either a simplex or a polyhedron defined by:*

$$\begin{array}{ll} \forall j \in \mathcal{I}_i \ , & x_j = (1-\alpha) z_j \\ \forall j \in \mathcal{O}_i \setminus \{j_0\} \ , & x_j = x_{j_0} \\ \forall j \in \mathcal{F}_i \ , & (1-\alpha) z_j \leq x_j \leq x_{j_0} \\ \quad \textit{and} & \sum_{j \in [n]} x_j = 1 \end{array}$$



- Implicitly defined actions: vertices of the polytope
- Concise description ⇒ polynomial time separation oracle ⇒ well-described polyhedron [Groetschel, Lovász, Schrijver, 1988]

# Well-described Markov Decision Processes

## Define

A well-described MDP is a finite MDP where the action sets are defined implicitly as the vertices of well-described polyhedra and the transitions and costs are linear

## Theorem

*The infinite horizon average cost problem on well-described MDP is solvable in polynomial time, even if there are exponentially many actions*

## Corollary

*The PageRank optimization problem with local constraints is solvable in polynomial time*

# Resolution by Dynamic Programming

- The ergodic dynamic programming equation
$$w_i + \psi = \max_{\nu \in \mathcal{P}_i} \nu(r_{i,\cdot} + w), \quad \forall i \in [n] \tag{1}$$
has a solution $(w, \psi) \in \mathbb{R}^n \times \mathbb{R}$. The constant $\psi$ is unique and is the value of the ergodic control problem
- To get an optimal strategy, select $\forall i$ a maximizing $\nu \in \mathcal{P}_i$

# Resolution by Dynamic Programming

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has a solution $(w, \psi) \in \mathbb{R}^n \times \mathbb{R}$. The constant $\psi$ is unique and is the value of the ergodic control problem
- To get an optimal strategy, select $\forall i$ a maximizing $\nu \in \mathcal{P}_i$
- The unique solution of the discounted equation
$$w_i = \max_{\nu \,:\, \alpha\nu + (1-\alpha)z \in \mathcal{P}_i} \alpha\nu(r_{i,\cdot} + w) + (1-\alpha) z r_{i,\cdot}, \forall i \in [n] \quad (2)$$
is solution of (1) with $\psi = (1-\alpha)zw$
- The fixed point scheme for (2) has contracting factor $\alpha$ independent of the dimension: complexity of optimization
$$O\Big(\frac{\log(\epsilon)}{\log(\alpha)} \sum_{i \in [n]} |\mathcal{O}_i| + |\mathcal{F}_i| \log(|\mathcal{F}_i|)\Big)$$

# Existence of a master page

## Theorem

*Assume* $\forall i, j,\ r_{i,j} = r'_i$ *and let* $v = (I_n - \alpha S)^{-1} r'$ *be the mean reward before teleportation*

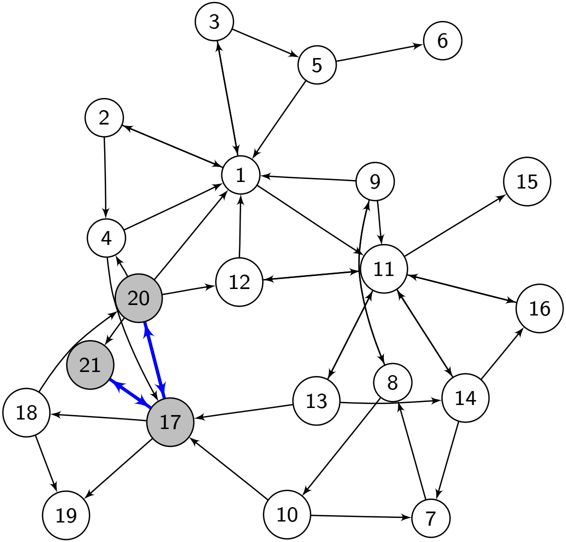
$P = \alpha S + (1-\alpha) ez$ *is an optimal link strategy if and only if*

$$\begin{cases} v_j > \frac{v_i - r_i}{\alpha} \Rightarrow \text{ facultative link } (i,j) \text{ is activated} \\ v_j < \frac{v_i - r_i}{\alpha} \Rightarrow \text{ facultative link } (i,j) \text{ is desactivated} \end{cases}$$

$v$ gives a total order of preference for page pointing

De Kerchove, Ninove and Van Dooren, 2008:
similar result when one only requires that there exists a path from every page of the site to the rest of the web

# Web graph optimized for PageRank




21 : controlled page

1 : non controlled page

added links

PageRank sum:
0.0997 → 0.1694

Clique is not optimal

# Conclusion for PageRank optimization

- Polynomial time solvability of the PageRank optimization problem
- Introduction of well-described Markov Decision Processes
- Very fast optimization algorithm based on value iteration
  For a problem with 413,639 pages and 2,319,174 facultative links, solution in 81s with Intel Xeon 2.98Ghz
- Qualitative results on the optimal strategies
- Application to spam detection by minimizing the PageRank of known spam pages and propagating "spamicity"

# Ranking algorithms

- Perron vector (Kendall and Babigton Smith 1939)
- HITS (Kleinberg 1998)
- SALSA (Lempel and Moran 2000)
- HOTS (Tomlin 2003)
- CenterRank (Blondel et al 2004)
- Matrix scaling (Smith 2005)
- ...

# Definition of HITS [Kleinberg, 1998]

- Given a query, we build a subgraph of the web graph, focused on the query
- Hub and authority scores

$$\rho\, hub_j = \sum_{i:j\to i} aut_i \qquad \rho\, aut_i = \sum_{j:j\to i} hub_j$$

- $A$: adjacency matrix of the subgraph: $A^T A\, aut = \rho^2 aut$
- Uniqueness guaranteed with $(A^T A + \xi e e^T)\, aut = \rho^2 aut$
- PageRank, SALSA and CenterRank also rank web pages according to a Perron vector

# Kleinberg's HITS optimization

Obligatory links $\mathcal{O}$, facultative links $\mathcal{F}$, prohibited links $\mathcal{I}$
$J$ is the set of hyperlinks selected, $N(x) = \sum_{i \in [n]} x_i^2$

The HITS optimization problem is:

$$\max_{J \subseteq \mathcal{F}, x \in \mathbb{R}_+^n} \{\varphi(x) \ ; \ (A(J)^T A(J) + \xi e e^T) x = \rho^2 x \ , \ N(x) = 1\}$$

Relaxed HITS optimization problem:
weighted adjacency matrices
$\rightarrow$ differentiable optimization

# Perron vector Optimization Problem

We study the following Perron vector Optimization Problem:

$$\max \; J(M) = \varphi(u(M)) \\ M \in h(C)$$

- $h : \mathbb{R}^m \to \mathbb{R}_+^{n \times n}$ and $\varphi : \mathbb{R}_+^n \to \mathbb{R}$ are differentiable
- $u : \mathbb{R}_+^{n \times n} \to \mathbb{R}_+^n$ is the function that to an irreducible matrix associates its normalized Perron vector
- $C$ convex, $h(C)$ a set of nonnegative irreducible matrices

# Chosen approach

- Nonconvex optimization problem
- Special case with $h$ and $\varphi$ linear and $C$ a polytope is already NP-hard
- We abandon global optimality: first order method
- But efficient and scalable computation

# Derivative for Perron vector optimization

## Proposition (Derivative has rank one)

*Denote $R = (M - \rho I_n)^{\#}$ the reduced resolvent at $\rho$ and $N$ the normalization function of $u$*

*Let $w^T = (-\nabla\varphi^T + (\nabla\varphi \cdot u)\nabla N^T)R$, then*

$$g_{ij} = \frac{\partial J}{\partial M_{ij}} = \nabla\varphi^T \frac{\partial u}{\partial M_{ij}} = w_i u_j$$

## Proof

Consequence of [Deutch and Neumann, 1985]
$\frac{\partial u}{\partial M_{ij}}(M) = -Re_i u_j + (\nabla N^T Re_i u_j)u$

# Iterative scheme for the derivative

## Proposition

*Let $M$ be a primitive matrix with Perron vectors $u$ and $v$.*
*We denote $\tilde{M} = \frac{1}{\rho}M$, $P = uv$, $z = \frac{1}{\rho}(-\nabla\varphi^T + (\nabla\varphi \cdot u)\nabla N^T)$*

*Then* $$w_{k+1} = (z + w_k\tilde{M})(I_n - P) \to w$$

*with a geometric rate of convergence $\frac{|\lambda_2|}{\rho}$*

- Direct application of Deutsch and Neumann formula: $O(mn^3)$
- Inversion of the linear system defining $w$: $O(n^3)$
- Iterative algorithm: $O(m+n)$ operations per iteration

# Coupled power and gradient iterations

- Approximation of value and gradient
  $M$ is a weighted adjacency matrix, $u_{k+1} = \frac{Mu_k}{N(Mu_k)}$
  $J_n(M) = \varphi(u_{k_n})$ and $g_n(M) = w_{k_n} u_{k_n}^T$ where $k_n$ is the first nonnegative integer $k$ such that $\|u_{k+1} - u_k\| \leq \Delta(n)$
- Gradient step rule
  $\mathcal{B}_n(M)$ is an interrupted Armijo line search that may fail
- Polak's Master algorithm model for precision control
  Let $\omega \in (0,1)$, $\sigma' \in (0,1)$, $n_{-1} \in \mathbb{N}$ and $M_0 \in \mathcal{C}$,
  For $i \in \mathbb{N}$, compute $M_{i+1}$ and the smallest $n_i \geq n_{i-1}$ s.t.

$$M_{i+1} \in \mathcal{B}_{n_i}(M_i)$$
$$J_{n_i}(M_{i+1}) - J_{n_i}(M_i) \leq -\sigma'(\Delta(n_i))^\omega$$

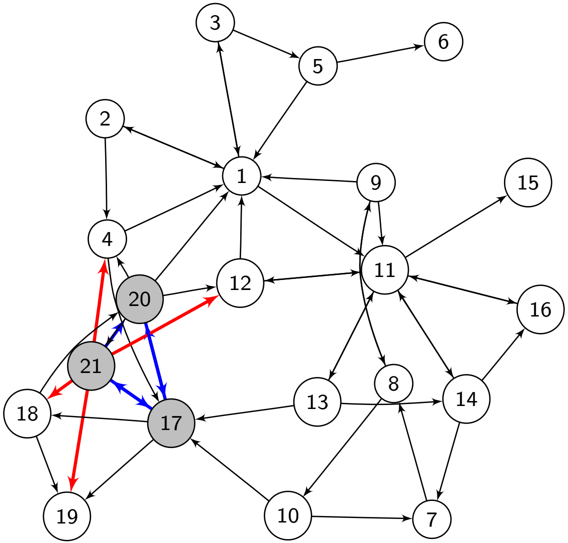
# Convergence

## Theorem

*Let $(M_i)_{i\geq 0}$ be a sequence constructed by the coupled power and gradient iterations for the resolution of the perron vector optimization problem*

*Then every accumulation point of $(M_i)_{i\geq 0}$ is a stationary point of the optimization problem.*

# Web graph optimized for HITS




added internal links
added external links

HITS authority sum:
$0.0555 \rightarrow 0.3471$

# Tomlin's ideal HOTS algorithm

Network flow model of web traffic
$A$ is the adjacency matrix of the web graph (first irreducible)
Web surfers minimize the entropy of the traffic

$$\max_{\rho \geq 0} \; -\sum_{i,j \in [n]} \rho_{i,j} \left(\log\left(\frac{\rho_{i,j}}{A_{i,j}}\right) - 1\right)$$

$$\sum_{j \in [n]} \rho_{i,j} = \sum_{j \in [n]} \rho_{j,i} \; , \; \forall i \in [n] \qquad (p_i)$$

$$\sum_{i,j \in [n]} \rho_{i,j} = 1 \qquad (\mu)$$

Optimal $\rho$ while PageRank gives a specific $\rho$
(uniform probability is arbitrary)

# Dual problem: irreducible case

Minimize:

$$\theta(p,\mu) := \sum_{i,j\in[n]} A_{ij} e^{p_i - p_j + \mu} - \mu$$

$\theta$ is convex and differentiable

$$\frac{\partial\theta}{\partial\mu}(p,\mu) = 0 \Rightarrow \mu = -\log\Big(\sum_{i,j\in[n]} A_{ij} e^{p_i - p_j}\Big)$$

$$\frac{\partial\theta}{\partial p}(p,\mu) = 0 \Rightarrow d = e^p \text{ is a fixed point of } f :$$

$$d_i = f_i(d) = \left(\frac{(A^T d)_i}{(A d^{-1})_i}\right)^{1/2}$$

$p_i$ is called the “temperature” of page $i$

# Tomlin's HOTS: handling reduciblity

Network flow model with constraints on the modified network

$$A' = \begin{bmatrix} A & 1 \\ 1^T & 0 \end{bmatrix}$$

$$\max_{\rho \geq 0} \; -\sum_{i,j \in [n+1]} \rho_{i,j} (\log(\frac{\rho_{i,j}}{A'_{i,j}}) - 1)$$

$$\sum_{j \in [n+1]} \rho_{i,j} = \sum_{j \in [n+1]} \rho_{j,i} \;, \; \forall i \in [n+1] \qquad (p_i)$$

$$\sum_{i,j \in [n+1]} \rho_{i,j} = 1 \qquad (\mu)$$

$$\sum_{j \in [n]} \rho_{n+1,j} = 1 - \alpha \qquad (a)$$

$$1 - \alpha = \sum_{i \in [n]} \rho_{i,n+1} \qquad (b)$$

# Dual function: general case

$$\theta(p, \mu, a, b) = \sum_{i,j \in [n]} A_{ij} e^{p_i - p_j + \mu} + \sum_{i \in [n]} e^{-b - p_{n+1} + p_i + \mu} + \sum_{j \in [n]} e^{a + p_{n+1} - p_j + \mu} - (1-\alpha)a - \mu + (1-\alpha)b$$

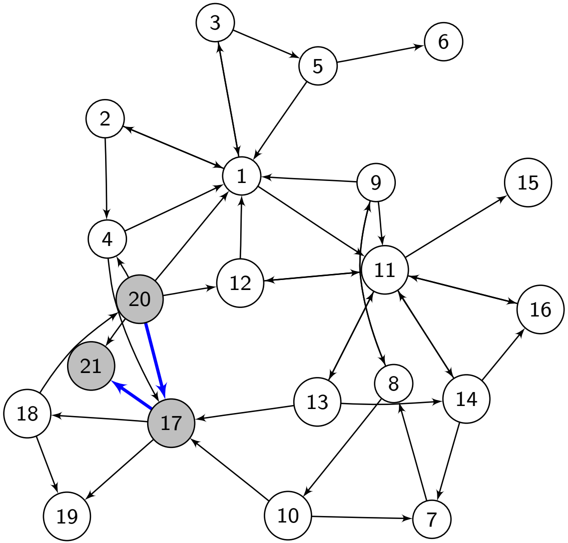
- Effective HOTS:

$$d_i = F_i(d) = \left( \frac{(A^T d)_i + e^{a(d)}}{(Ad^{-1})_i + e^{-b(d)}} \right)^{1/2}$$

## Proposition (HOTS optimization)

*Assuming the HOTS algorithm $d^{k+1} = F(d^k)$ converges, the coupled power and gradient iterations converges to a stationary point of the HOTS optimization problem*

# Web graph optimized for HOTS





HOTS score sum:
$0.142 \to 0.169$

Page 21 has no outlink

# Convergence of the ideal HOTS algorithm

Ideal HOTS vector defined by

$$d_i = f_i(d) = \left( \frac{(A^T d)_i}{(A d^{-1})_i} \right)^{1/2}$$

## Proposition

*If $A$ is irreducible and $A + A^T$ is primitive, then the ideal HOTS algorithm $d^{k+1} = f(d^k)$ converges to the ideal HOTS vector (unique up to a multiplicative constant)*

# Proof of convergence

## Proof

$f_i(d) = \left(\frac{(A^T d)_i}{(Ad^{-1})_i}\right)^{1/2}$

$f$ is monotone: $d_1 \geq d_2 \Rightarrow f(d_1) \geq f(d_2)$
$f$ is homogeneous: $\lambda \in \mathbb{R}_+ \Rightarrow f(\lambda d) = \lambda f(d)$

$A$ irreducible $\Rightarrow G(f)$ is strongly connected $\Rightarrow f$ has an eigenvector $(f(d^*) = \mu d^*)$ [Gaubert, Gunawardena 2004]

$A$ irreducible $\Rightarrow \frac{\partial f}{\partial d}(d^*)$ irreducible $\Rightarrow$ eigenvector is unique [Nussbaum, 1988]

$A + A^T$ primitive $\Rightarrow \frac{\partial f}{\partial d}(d^*)$ primitive
$\Rightarrow$ power algorithm converges [Nussbaum, 1988]

# Convergence of the effective HOTS algorithm

## Theorem

*If there exists a feasible point with the same pattern as $A$, then the HOTS algorithm converges to the HOTS vector $d^*$ s.t. $d^*_i = F_i(d^*) = \left(\frac{(A^T d^*)_i + e^{a(d^*)}}{(A(d^*)^{-1})_i + e^{-b(d^*)}}\right)^{1/2}$ (unique up to a multiplicative constant) with a linear rate of convergence equal to $|\lambda_2(\nabla F(d^*))|$.*

## Proof

$F$ is homogeneous but not monotone: special proof required

The ideal HOTS operator verifies $\theta(\log(f(d)), 0) \leq \theta(\log(d), 0)$: Lyapounov function

All the eigenvalues of $\nabla F(d^*)$ belong to $(-1, 1]$ and eigenvalue 1 is simple: local contraction in projective space

# Drawbacks of HOTS

- $d_i = f_i(d) = \left( \frac{(A^T d)_i}{(Ad^{-1})_i} \right)^{1/2}$

  Relaxation of Perron ranking $\rho d = A^T d$
  (a good page is a page pointed to by good pages)
  and anti-Perron ranking $\rho^{-1} d_i = \frac{1}{(Ad^{-1})_i}$
  (a bad page is a page that points to bad pages)

  But anti-Perron penalizes pointing even to good pages

- Convergence rate may deteriorate when the size of the web graph grows:

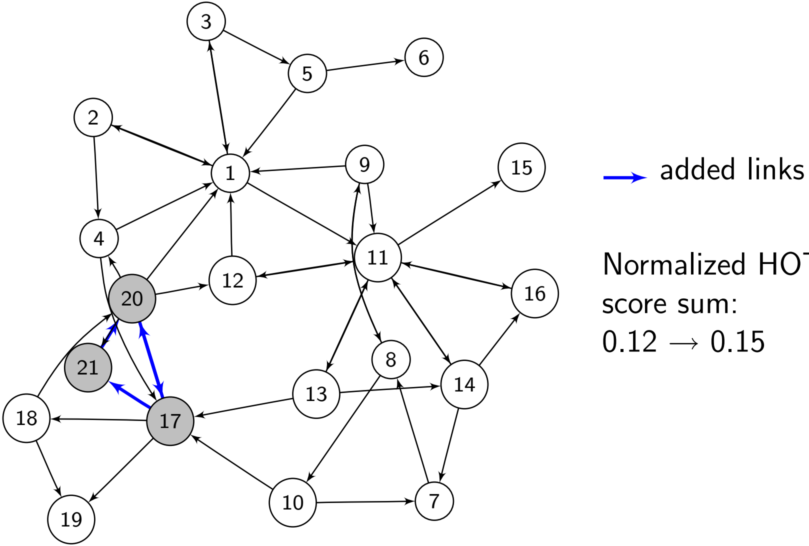
| | CMAP 1,500 p | NZ Uni 413 kp | uk2002 18 Mp |
|---|---|---|---|
| $\lvert\lambda_2(\nabla F)\rvert$ | 0.946 | 0.995 | 0.9994 |

# Normalized HOTS

- Normalization of the adjacency matrix $M_{i,j} = \frac{A_{i,j}}{\sum_k A_{i,k}}$
- Relative entropy function
- Dangling nodes dealt with an additional fictitious node
- No more penalty for pointing to good pages: a bad page is a page that, in the mean, points to bad pages
- Better experimental convergence rate:

| | CMAP 1,500 p | NZ Uni 413 kp | uk2002 18 Mp |
|---|---|---|---|
| $\lvert\lambda_2(\nabla F)\rvert$ | 0.906 | 0.988 | 0.960 |

# Web graph optimized for Normalized HOTS




Normalized HOTS score sum:
$0.12 \rightarrow 0.15$

# Comparison of web ranking algorithms

| Algorithm | convergence rate | external links | harder than PR to manipulate |
|---|---|---|---|
| Perron | good | ++ | - - - |
| PageRank | 0.85 | - | reference |
| HITS | good | +++ | - - - |
| SALSA | good | + | - - |
| HOTS | bad | - - | + (?) |
| Normalized HOTS | acceptable (?) | = | + (?) |

Performances of web ranking algorithms

+ good characteristic

= average

- bad characteristic

(?) experimental likelihood only

# From web ranking to chronotherapeutics

- For the web, scalability issues are very important
- So we developped a scalable optimization algorithm for Perron vector optimization
- Other situation where scalability is important:

  nonnegative matrices arise from monotone discretizations of age-structured Partial Differential Equations
- Optimization of chemotherapy infusion schedules [Basdevant, Clairambault, Lévi, 2006]

  Minimize the number of cancer cells while keeping the number of healthy cells above a toxicity threshold

# Cancer chronotherapeutics

- Circadian clocks control cell proliferation
- Different behaviours (healthy or cancer cells)
- Chronotherapy [Lévi, 2002]

  Drug infusion schedules that depend on time
- [Billy, Clairambault, Fercoq, Gaubert, Lepoutre, Ouillon, Saito, Mathematics and Computers in Simulation 2011]

# The cell cycle

Cell proliferation: 4 main phases

5-FluoroUracil (5-FU):
DNA damage in phase S

Proliferation stopped
at the G2/M checkpoint

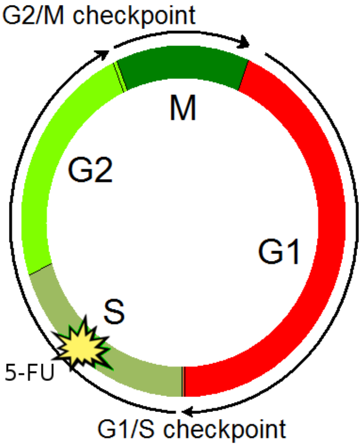



Figure: The cell cycle
G1: 1st growth phase, S: DNA synthesis
G2: 2nd growth phase, M: mitosis
Green and red correspond to the color
of the nucleus with FUCCI reporters

# McKendrick age-structured population model

$$\frac{\partial n_i(t,x)}{\partial t} + \frac{\partial n_i(t,x)}{\partial x} + \big(d_i(t,x) + K_{i\to i+1}(t,x)\big)n_i(t,x) = 0$$

$$n_{i+1}(t,0) = \int_0^\infty K_{i\to i+1}(t,x)n_i(t,x)dx$$

$$n_1(t,0) = 2\int_0^\infty K_{I\to 1}(t,x)n_I(t,x)dx$$

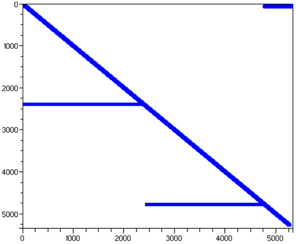
If $d$ and $K$ are $T$-periodic: Floquet eigenvalue $\lambda$

$$n_i(t,x) \sim C^0 N_i(t,x)e^{\lambda t}$$

$N_i$ is bounded and $T$-periodic

# Block Leslie model

After a monotone discretization, we get an age-structured population with ages $1, \dots n$

$M^k =$ 

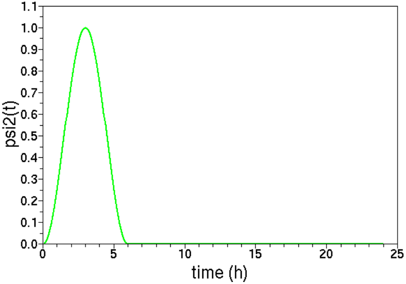

$$n^{k+1} = M^k n^k \ , \quad \mathbf{M} = M^{N_T - 1} \dots M^1 M^0 \ , \quad n^T = \rho n^1 = \mathbf{M} n^1$$

$\frac{1}{T} \log(\rho)$ : approximate growth rate of the population
$\rho \geq R$: viability constraint

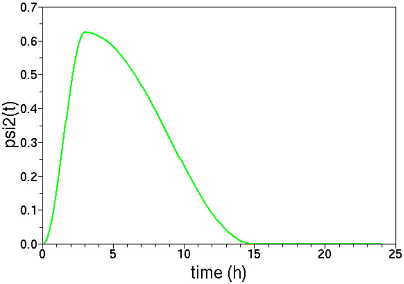
# Modelling cancer cells

Two independent populations with the same model
$K_{2\to3}(x,t) = \kappa_{2\to3}(x).\psi_2(t)$

Less synchronized proliferation gives an increased growth rate [Altinok, Lévi, Goldbeter, 2007]




Circadian control for healthy cells




Circadian control for cancer cells

# Floquet eigenvalue optimization problem

Control: $K_{2\to 3}(x,t) = \kappa_{2\to 3}(x).\psi_2(t).(1-g(t))$
$g(t) = 0$: no drug
$g(t) = 1$: transition blocking infusion
5-FU acts on phase $S$, thus on the $G_2/M$ checkpoint only

$$\min_{g(\cdot)} \lambda_C(g)$$

$$\lambda_H(g) \geq \Lambda$$

$$g \text{ 24h-periodic}$$

Optimal long term viable chemotherapy infusions

# Discretized optimization problem

Discretized systems for cancer and healthy cells:
nonnegative matrices $\mathbf{M}_C(x)$ and $\mathbf{M}_H(x)$

$$\min_{x \in [0,1]^{N_T}} \frac{1}{T} \log \left( \rho(\mathbf{M}_C(x)) \right)$$

$$\frac{1}{T} \log \left( \rho(\mathbf{M}_H(x)) \right) \geq \Lambda$$

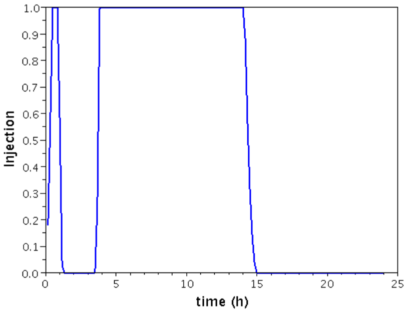
## Proposition

*The coupled power and gradient algorithm can be adapted to this case*

## Proof

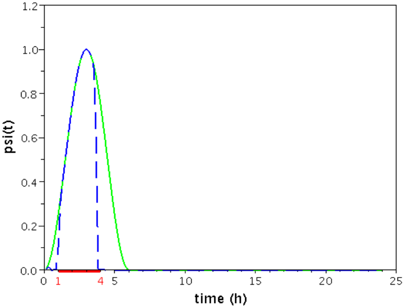
$\frac{\partial \rho}{\partial \mathbf{M}_{i,j}} = u_i v_j$ and constraint dealt with a multiplier's method

# Locally optimal strategy

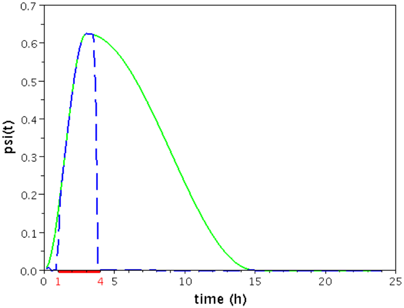



24h-periodic drug infusions $g(t)$

# Locally optimal strategy




Action of drug infusion on transition rate for healthy cells




Action of drug infusion on transition rate for cancer cells

$G_2/M$ transition rate without drug $\psi_2(t)$
Drug induced transition rate $\psi_2(t)(1-g(t))$

Under the locally optimal strategy found, transitions $G_2/M$ are restricted to lie between 1 a.m. and 4 a.m.

# Conclusion chronotherapeutics

- We modelled a chemotherapy optimization problem with an age-structured proliferation model
- Optimization problem with periodic controls
- Optimization of chemotherapy shows the interest of chronotherapy
- Work in progress: Combination with a more realistic drug pharmacokinetics and pharmacodynamics model

# Conclusion

- PageRank optimization: ergodic control
  very fast scalable algorithm for global optimum
- Other web rankings: small rank property of derivatives
  scalable optimization algorithm (but only local optimality)
- Convergence of HOTS
- Application of Perron vector optimization to chronotherapeutics
- Main open problem: determination of bounds
  for the Perron value optimization problem