The Mathematics and Statistics of Infectious Disease Outbreaks

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L9: Univariate outbreak detection[1]

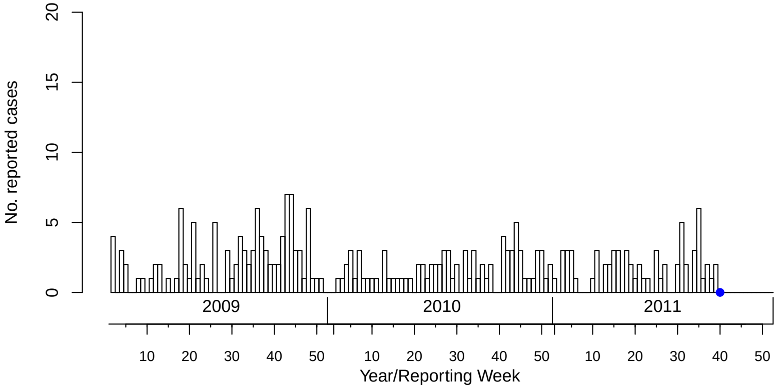
[1]LaMo: 2020-08-06 @ 15:53:31

Overview

Outline

Example: Monitoring German Salmonella Newport Cases

German Infection Protection Act (IfSG) data from the Robert Koch Institute (up to W40-2011):



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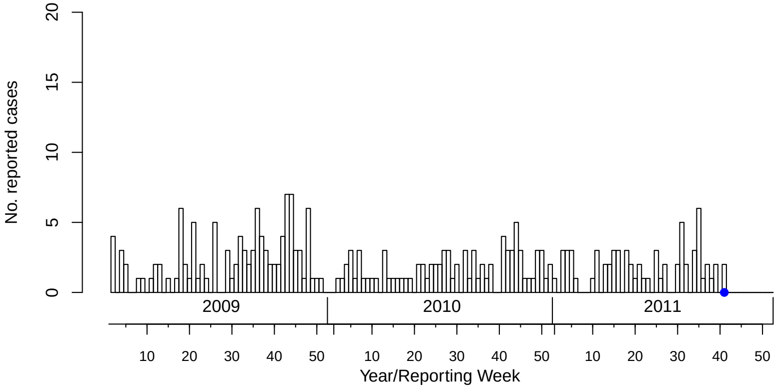

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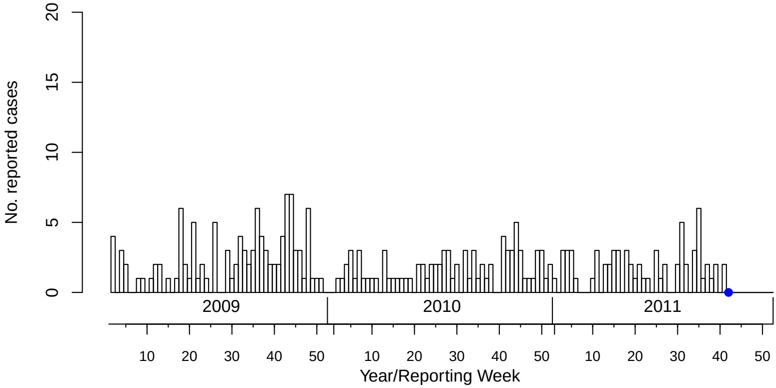

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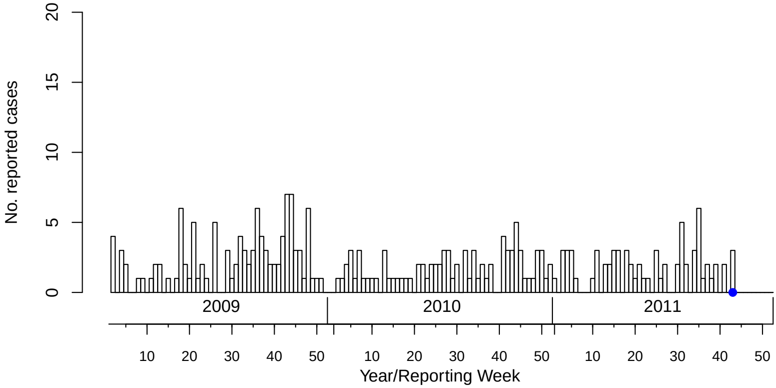

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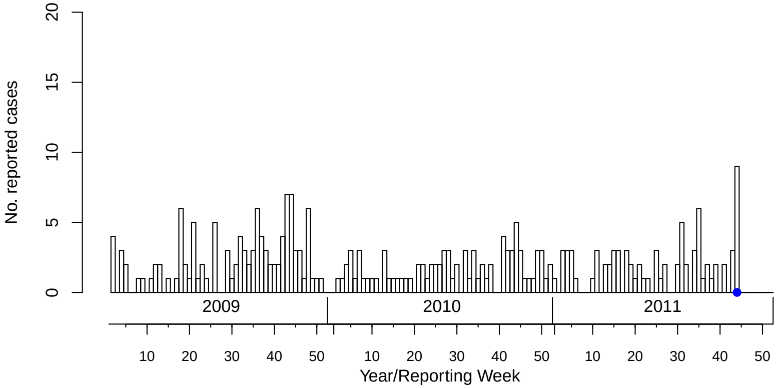

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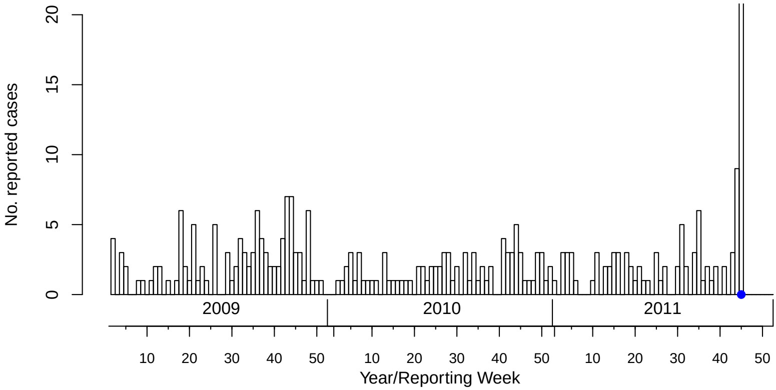

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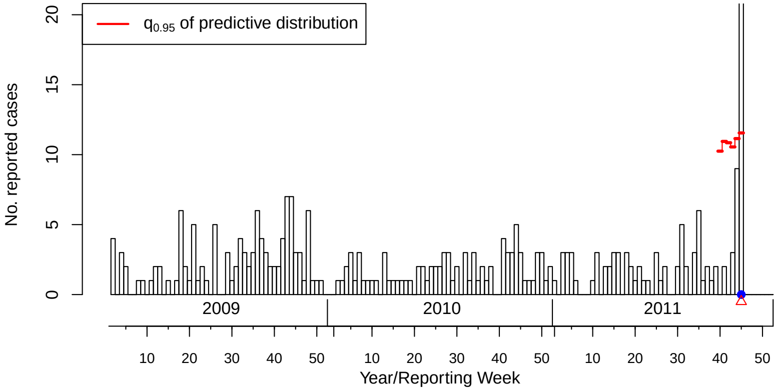


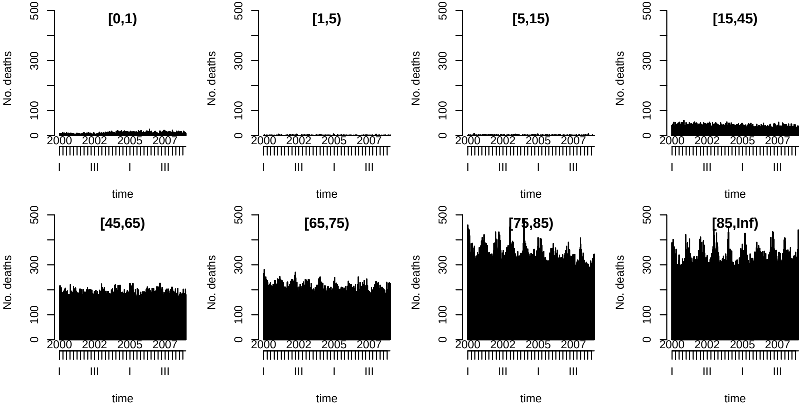
During Oct-Nov 2011 there was an outbreak associated with mung bean sprouts (RKI, 2012)

Example – The EuroMOMO project (1)

- European monitoring of excess mortality for public health action (EuroMOMO)
- Aim: develop and strengthen real-time monitoring of mortality across Europe in order to enhance the management of serious public health risks such as pandemic influenza, heat waves and cold snaps
- Main outcome of mortality monitoring: excess mortality
- In this course: Focus on monitoring aspect

Example – The EuroMOMO project (2)

Weekly danish mortalities 2000-2008 in 8 age-groups as provided by Statens Serum Institute (Höhle and Mazick, 2010).



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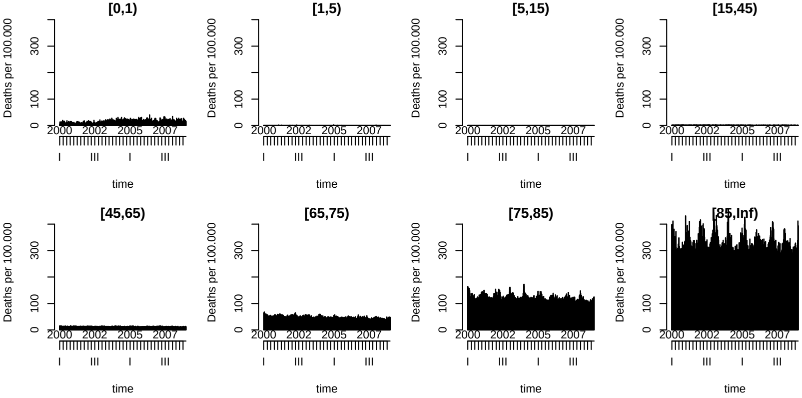

Outline

1. Monitoring of univariate count data time series
   - Statistical Framework for Aberration Detection
   - Simple Algorithm for Ad-Hoc Detection
   - Farrington algorithm and beyond

Statistical Framework for Aberration Detection (1)

- Univariate time series $\{y_t,\ t = 1, 2, \ldots\}$ to monitor
- For each time t we differentiate between two underlying states: in-control (everything is fine) or out-of-control (something is wrong).
- At time $s \geq 1$, the available information is $\boldsymbol{y}_s = \{y_t\ ;\ t \leq s\}$.
- Based on $\boldsymbol{y}_s$ an automatic detection procedure has to decide if there is unusual activity at time s (or not).

Statistical Framework for Aberration Detection (2)

- The detectors are initially only based on the one-step-ahead predictive distribution at each time point (Shewhart-like control chart):
  - Let $G(y_s|y_1,\ldots,y_{s-1};\boldsymbol{\theta})$ be the distribution of Y_s in case everything is in-control.
  - If the actual observed value $Y_s = y_s$ is extreme in G, this is evidence against things being in-control.
  - The alarm threshold $a_{1-\alpha,s}$ at each time point is calculated as the $(1-\alpha)$'th quantile of the predictive distribution. If $y_s > a_{1-\alpha,s}$ then we have an alarm.
- This can be generalized to more sequential control charts accumulating information, e.g. cumulative sum (CUSUM) methods.

Intermezzo: Estimation, prediction and uncertainty

- Data $\boldsymbol{y}$ are the observed value of a random variable $\boldsymbol{Y}$ characterized by a parametric model with density $f(\boldsymbol{y};\boldsymbol{\theta})$.
- Aim: predict the value of a random variable $\boldsymbol{Z}$, which, conditionally on $\boldsymbol{Y}=\boldsymbol{y}$ has distribution function $G(\boldsymbol{z}|\boldsymbol{y};\boldsymbol{\theta})$, *depending on* $\boldsymbol{\theta}$.
- Simplest form of the prediction problem:

$$Y_1,\ldots,Y_n \overset{\text{iid}}{\sim} f(y;\boldsymbol{\theta}),$$

  and the task is to predict $Z=Y_{n+1}$.
- In *time series 1-step-ahead prediction* the observations are correlated and the aim is to predict $\boldsymbol{Z}=Y_{n+1}$.

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Example: Predicting a new $N(\mu, \sigma^2)$ observation (1)

- Let $Y_1, \ldots, Y_n \stackrel{\text{iid}}{\sim} N(\mu, \sigma^2)$ with unknown μ and σ^2. Then

$$\frac{Y_{n+1} - \overline{Y}}{s\sqrt{1 + \frac{1}{n}}} \sim t(n-1),$$

  where $\overline{Y} = \frac{1}{n}\sum_{i=1}^{n} Y_i$ and $s^2 = \frac{1}{n-1}\sum_{i=1}^{n}(Y_i - \overline{Y})^2$ are the sample mean and sample variance of $\boldsymbol{Y}$, respectively.

- A $(1-2\alpha)\cdot 100\%$ two-sided **prediction interval** (PI) is thus given by

$$\overline{Y} \pm t_{1-\alpha}(n-1) \cdot s \cdot \sqrt{1 + \frac{1}{n}}.$$

Example: Predicting a new $N(\mu, \sigma^2)$ observation (2)

- A *plug-in* $(1-2\alpha)\cdot 100\%$ two-sided **prediction interval** for Y_{n+1} is:

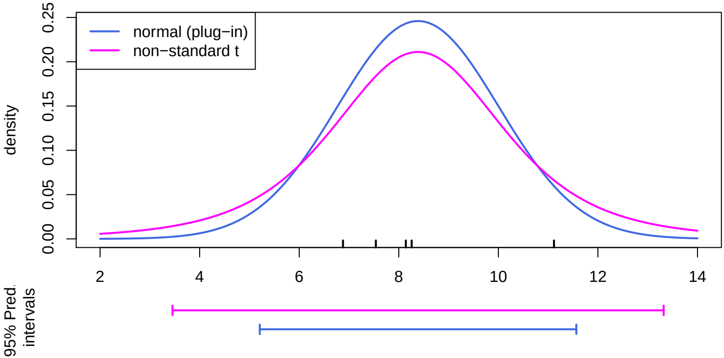
$$\overline{Y} \pm z_{1-\alpha} \cdot s.$$

- Both of these are not to be confused with a $(1-2\alpha)\cdot 100\%$ two-sided **confidence interval** for μ:

$$\overline{Y} \pm z_{1-\alpha} \cdot \frac{s}{\sqrt{n}}.$$

Example: Predicting a new $N(\mu, \sigma^2)$ observation (3)

- Illustration: PIs based on $n = 5$ observations from $N(\mu, \sigma^2)$.



- For $n = 5$ the 95% plug-in PI corresponds to a 85% PI. The 95% CI for μ is 7.2–9.6, which only corresponds to a 46% PI.

Summary: Ad-Hoc Outbreak Detection Algorithm

- Predict value y_s at time $s = (s^w, s^y)$ using a set of reference values from window of size $2w + 1$ up to b years back.
- Let $n = b(2w + 1)$ and compute threshold as the upper 97.5% quantile of the predictive distribution for y_s, i.e.

$$a_{0.975,s} = \overline{y} + t_{0.975}(n-1) \cdot s \cdot \sqrt{1 + \frac{1}{n}}.$$

- Sound alarm, if $y_s > a_{0.975,s}$.

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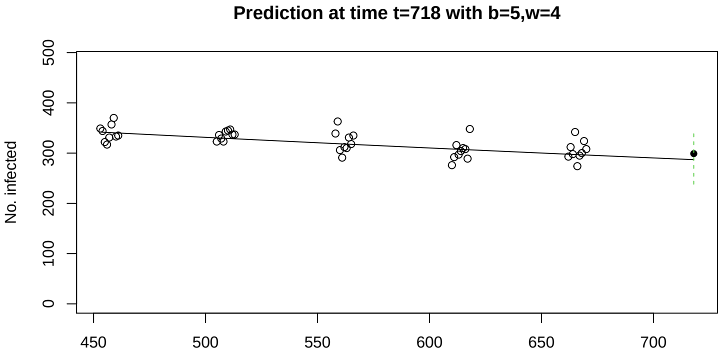
Challenges of surveillance data

Issues making the statistical modelling and monitoring of surveillance time series a challenge:

- Lack of clear case definitions
- Under-reporting and reporting delays
- Often no denominator data
- Seasonality
- Low number of reported cases
- Presence of past outbreaks
- Existence of concurrent “explanatory” processes

Farrington algorithm (1) – basic model

- Predict value y_s at time $s = (s^w, s^y)$ using a set of reference values from window of size $2w + 1$ up to b years back.



- Fit overdispersed Poisson generalized linear model (GLM) to the $b(2w + 1)$ reference values where $E(y_t) = \mu_t$, $\text{Var}(y_t) = \phi \cdot \mu_t$ with $\log \mu_t = \alpha + \beta t$ and $\phi > 0$.

Farrington algorithm (2) – outbreak detection

Predict and compare:

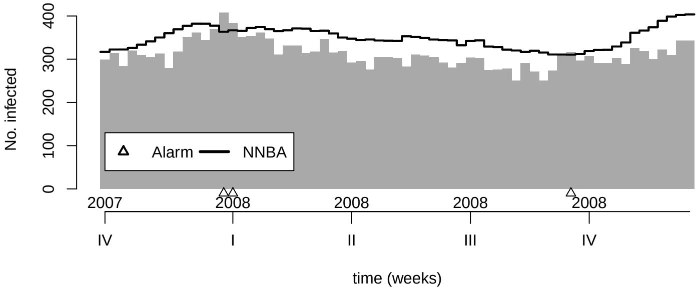
- An approximate $(1-\alpha)$ one-sided prediction interval for y_s based on the GLM has upper limit $a_{1-\alpha,s} = \hat{\mu}_s + z_{1-\alpha} \cdot \sqrt{\text{Var}(y_s - \hat{\mu}_s)}$
- If the oserved y_s is greater than $a_{1-\alpha,s}$, then flag s as outbreak

Refinements of the algorithm include:

- Computation of the prediction interval on a transformed scale
- Use a re-weighted fit with weights based on Anscombe residuals in order to correct for outliers
- Low count protection

Application: Danish mortality data (age group 75-84 years)

- Results of the old and improved Farrington algorithm, respectively, with $w = 4$, $b = 5$ and $\alpha = 0.005$ starting at W40-2007:



Outline

System Design

- Salmon, Schumacher, and Höhle (2016) describes a system integrating outbreak detection algorithms into the epidemiological workflow

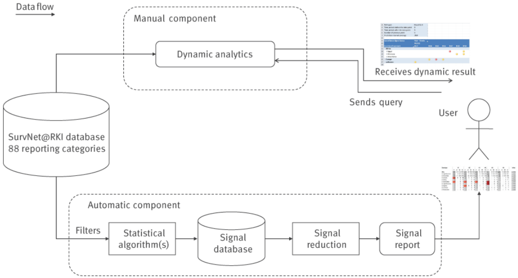


Figure source: Salmon, Schumacher, and Höhle (2016)

- Example of using machine learning methods for the more than 30,000 time series

Application on Salmonella Montevideo 2009-2010

Results from the extended Farrington procedure using last five years as reference values:

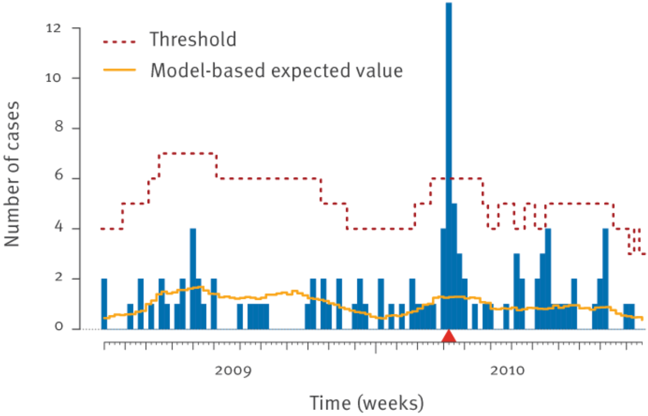


Figure source: Salmon, Schumacher, and Höhle (2016)

Salmonella Report for W41–46 of 2013

Weekly Report at National Level:

Serotype	Week 41				Week 42				Week 43				Week 44				Week 45				Week 46			
	y_t	o_t	μ_t	U_t	y_t	o_t	μ_t	U_t	y_t	o_t	μ_t	U_t	y_t	o_t	μ_t	U_t	y_t	o_t	μ_t	U_t	y_t	o_t	μ_t	U_t
Salmonella, all serotypes	466	27	512	691	373	23	485	650	370	16	461	620	356	15	439	601	411	8	417	580	290	14	390	540
S. Typhimurium	107	2	151	221	103	1	145	214	108	2	140	208	106	5	134	202	142	4	127	191	90	4	120	181
S. Enteritidis	158	11	154	230	123	12	142	212	115	11	131	194	84	4	124	189	80	1	116	182	62	2	107	168
S. Infantis	**25**	**6**	**9**	**18**	16	3	8	17	8	1	8	18	10	-	8	17	2	-	7	17	5	-	7	16
S. Derby	4	NA	5	11	2	NA	5	11	7	NA	5	11	3	NA	5	11	4	NA	5	11	1	-	5	11
S. Manhattan	**7**	**NA**	**0**	**2**	**4**	**NA**	**0**	**2**	**4**	**NA**	**0**	**2**	**3**	**NA**	0	**2**	**3**	**NA**	**0**	**2**	NA	NA	0	2
S. Typhimurium, monophasic	2	NA	0	2	2	NA	0	2	2	NA	0	2	**6**	**NA**	0	**2**	**5**	**NA**	**0**	**3**	3	NA	0	3
S. Agona	2	NA	1	4	**7**	**4**	**1**	**4**	2	1	1	4	3	2	1	4	1	NA	1	4	3	2	1	4
S. Virchow	4	NA	3	8	1	NA	3	8	3	NA	3	7	1	NA	3	7	5	1	3	7	1	NA	3	7
S. Muenchen	3	NA	1	4	3	NA	1	4	NA	NA	1	4	3	NA	1	4	2	NA	1	4	NA	NA	1	4

Table source: Salmon, Schumacher, and Höhle (2016)

Outline

Discussion

- The presented methods are implemented in the R package `surveillance` (Salmon, Schumacher, and Höhle, 2016)
- Developing, maintaining and improving automatic outbreak detection systems is an interdisciplinary activity!
  - Even more work could be put into user adaptation.
  - Delay adjusted monitoring (Salmon, Schumacher, Stark, et al., 2015)
- The system proved to be a good insurance against missing anything important – see e.g. Gertler et al. (2015)

Literature I

Gertler, Maximilian et al. (2015). "Outbreak of cryptosporidium hominis following river flooding in the city of Halle (Saale), Germany, August 2013". In: *BMC Infectious Diseases* 15.1, p. 88. ISSN: 1471-2334. DOI: 10.1186/s12879-015-0807-1. URL: http://www.biomedcentral.com/1471-2334/15/88.

Höhle, M. and A. Mazick (2010). "Aberration detection in R illustrated by Danish mortality monitoring". In: *Biosurveillance: A Health Protection Priority*. Ed. by T. Kass-Hout and X. Zhang. CRC Press, pp. 215–238.

RKI (2012). "Salmonella Newport-Ausbruch in Deutschland und den Niederlanden, 2011". In: *Epidemiologisches Bulletin* 20. Available as http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2012/Ausgaben/20_12.pdf, pp. 177–184.

Literature II

Salmon, M., D. Schumacher, and M. Höhle (2016). "Monitoring Count Time Series in R: Aberration Detection in Public Health Surveillance". In: *Journal of Statistical Software* 70.10. Also available as vignette of the R package surveillance. DOI: 10.18637/jss.v070.i10.

Salmon, M., D. Schumacher, K. Stark, and M. Höhle (2015). "Bayesian outbreak detection in the presence of reporting delays". In: *Biometrical Journal* 57.6. http://dx.doi.org/10.1002/bimj.201400159, pp. 1051–1067.