

SCI-Base: An Open-Source Spinal Cord Injury Animal Experimentation Database

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To capture all pertinent data during spinal cord injury animal experimentation, the authors have designed and implemented a database that is available for use under a public license. Their goals were to record all daily medical care of paraplegic animals, including unexpected complications; to store all injury parameters and/or therapeutic procedures; to track locomotor scores and other measures of functional recovery; to allow planning and management of experiments; and to serve as an externally linkable, SQL-queryable data mining source. Ultimately, the use of databases such as this will allow multiple neurotrauma laboratories to compare animal data through web meta-analysis.

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Spinal cord injury (SCI) affects 250,000 patients in the United States with approximately 49,000 new cases each year. The loss of motor and sensory function leads to great challenges for affected individuals. A large number of SCI patients develop serious secondary health problems and require extensive health care. Over the past 10 years, there has been considerable progress made in the search for treatments or cures for paralysis, mostly based on well-standardized laboratory animal models. One of these, the Multicenter Animal Spinal Cord Injury Study (MASCIS) contusion model (described later), has become a common tool at more than 150 laboratories throughout the world and has proved to correlate well with human injury¹. Laboratories investigating neuroprotective and regeneration therapies often require dozens to hundreds of animals per study and require a thorough archive of all data as well as detailed daily care records for later evaluation. We have created SCI-Base to fulfill this need.

MASCIS Model of Spinal Cord Injury

The MASCIS impactor, formerly known as the NYU impactor, is a device designed to deliver reproducible spinal contusions to rats. The basic design arose from a long tradition of weight-drop SCI models (e.g., see ref. 2), but Young and colleagues modified it in 1991 to include several functional improvements³⁻⁵. The most important modifications were the addition of digital potentiometers to measure impact head position and time precisely. Specific protocols for using the device were incorporated into the MASCIS project, which accumulated validation data relating distance of weight drop to several injury parameters,

including lesion volumes, spared white matter, and hindlimb locomotor function. Basso et al. developed the widely used Basso-Beattie-Bresnahan (BBB) locomotor scoring system for use with the MASCIS impactor^{6,7}. The MASCIS project validated the use of methylprednisolone in animals^{8,9}, which led to successful human trials and broad acceptance of this therapy¹⁰. Approximately 150 laboratories throughout the world now use the MASCIS device in spinal cord research. The MASCIS model is probably the most reproducible, widely used model of CNS trauma.

The MASCIS model procedure uses both male and female rats at 77 ± 5 days old (Long-Evans, originally obtained from Simonsen Laboratories, Inc., Gilroy, CA). Animals receive anesthesia consisting of pentobarbital (i.p., 45 ± 5 mg/kg for females and 65 ± 5 mg/kg for males) 1 h before undergoing a T9-10 laminectomy and subsequent securing of the vertebral column by clamping the T8 and T11 dorsal processes into the frame of the MASCIS impactor. The technician drops the 10.0-g weight 6.25, 12.5, 25, or 50 mm, and then records the impact velocity (ImpV), cord compression distance (Cd), compression time (Ct), and compression rate ($Cr = Cd/Ct$) are recorded. Paraplegia is immediate. Impact parameters outside of defined standards call for removal of an animal from the study.

The MASCIS model includes detailed protocols for postsurgical care. Animals receive antibiotics such as cephalosporin as needed for wound infections, and Baytril (enrofloxacin, Bayer Animal Health, Shawnee Mission, KS) for urinary tract infections. Each animal receives manual bladder expression once or twice daily for about two weeks or until they void sponta-

neously. Several complications sometimes occur, and for each complication there is a defined treatment regimen. For example, animals occasionally display autophagy, in which they will chew through skin, sometimes into muscle tissue, in response to peripheral pain or allodynia. Our laboratory has developed a scoring system and treatment therapy for this complication⁴. Acetaminophen usually relieves the symptoms of this behavior. Similarly, complications of bladder function have occurred, such as blood in urine or calcifications. Other complications include dehydration, decubiti, symptoms of stress, and a general failure to thrive.

Several parameters go on record as part of the standard MASCIS model. Many laboratories have added assays to the standard list, or they may only use a subset of the standard parameters. Foremost among the standard parameters is the BBB score^{6,7}, which assigns specific numeric scores to a detailed range of observable hindlimb locomotor motions, and parametric tests of this score have been proven to be valid¹¹. Other workers have described locomotion assays, including an inclined climbing test, induced standing on hindlimbs, and many other variations. Additional behavioral outcome measurements may include assessment of pain hypersensitivity or allodynia¹². Biochemical assays require recovery of the spinal cord tissue and homogenization for measuring tissue potassium, a sensitive index of surviving cell number, and, hence, lesion volume^{3,13}. Many laboratories also use histology or gene expression^{14,15}. Frequent additions include new behavioral, physiological, and biochemical outcomes.

Database Design

Our Center intends to conduct large-scale animal testing of promising therapies for SCI. With the growing number of animals to be tracked and the variety of requirements for data storage and reporting, we chose to begin a database design and implementation project using entirely open-source tools, so the resulting code can be customizable with little or no expense.

We selected the robust platform known as LAMP (the Linux operating system, Apache web server, MySQL database server, and PHP web scripting language). For each step of function, a web client (such as Internet Explorer or Mozilla) communicates with the Apache web server running on a Linux computer. The web page contains PHP scripting language, the program is interpreted on the server, and the PHP program interacts with the MySQL database server program. The result is a custom-configured web page displayed on the client computer. This platform is a common solution for open-source projects (see, for example, <http://sourceforge.net>). The programming process benefits from the availability of many other open-source projects both as examples of code design and as fully functional modules that may be incorporated into new open-source projects. For example, in our project we were able to incorporate JGraph (<http://www.aditus.nu/jgraph>) objects to create dynamic and highly customizable graphs within web pages. The focus on a web interface allows use of a broad variety of client solutions, including desktops of any operating system, hand-held computers, and portable laptops. We prefer the use of the open-source web client Mozilla (<http://www.mozilla.org>) to Microsoft's Internet Explorer because it displays simple HTML code with more tolerance for minor HTML/JavaScript errors. Although the server components are designed for Linux, one can run them on any Unix variant (including Mac OS X, which is our current production server) and Microsoft Windows. Finally, we do all processing on the powerful server computer, reducing hardware restrictions on the client. The use of the server-side scripting language PHP provides a seamless interface to the MySQL database and retains all secure data on the server, releasing only authorized data for display on the client computer over the public network. We currently restrict access to data transmission using a firewall to protect our laboratory subnet. Future versions will encrypt all data transmission using secure sockets layer (SSL). SSL uses a 'pub-

lic key-private key' encryption scheme that is built into all web browsers and servers to keep transmissions from being intercepted and read by a third party. Finally, some functions are provided to the client computer through JavaScript. The use of JavaScript allows for interactive functions on the client computer when there is no communication with the server. Our design goal was to create an interface that is as simple as possible, while keeping data stored in a flexible, sophisticated schema. This should encourage continued use of the database to collect daily events, yet allow for creative analysis of data after collection.

System Requirements

The server computer that is required for hosting the database and web server system does not need to be a sophisticated or powerful computer. One of our installations is a Windows 2000 laptop running on a 500-MHz processor. Our recommendation is a standard Intel-compatible computer (1 GHz or better) with at least 512 Mb of random access memory (RAM). The size of the project dictates storage space, but most standard (≥ 10 Gb) hard drives should be sufficient. The preferred operating system is Linux, but we have also installed successfully on Macintosh OS X and Windows 2000. Required software includes Apache (<http://www.apache.org>), MySQL (<http://www.mysql.com>), and PHP (<http://www.php.net>). The PHP version must include the graphics library GD (standard in a Linux binary distribution, available as an optional dll file for Windows). Additionally, we use the PHP graphing object library JGraph (<http://www.aditus.nu/jgraph>).

The client may be any desktop computer running Windows, Linux, Unix, or Mac OS X. We recommend the Mozilla web client (<http://www.mozilla.org>). We currently use a 'tablet' computer containing both an electromagnetic stylus for pen input and a folding keyboard. This computer contains wireless (802.11 b) networking to communicate with the server. This lightweight, portable computer is convenient for carrying through animal quarters

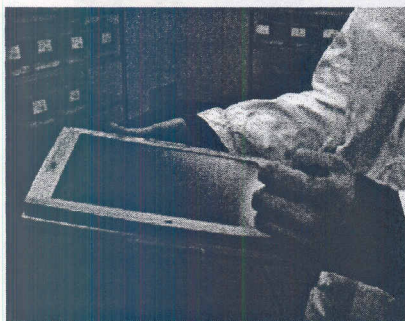


FIGURE 1. A lightweight tablet PC is useful for data input. Animal care staff use a small, portable, wireless (802.11 b) computer running Windows XP Tablet Edition.

for immediate data review or input (Fig. 1). One could use any wireless device with web capabilities, including hand-held (Palm or Windows Mobile PC) computers.

Obtaining SCI-Base

The entire software package is available under the GNU general public license (<http://www.gnu.org/licenses/gpl.html>). An installable package of source code and full directions are downloadable from <http://www.sci-base.org>. We ask that users register before downloading to provide users with notification of upgrades and to support our reports to our funding agency. The download includes PHP files, a SQL schema file to create empty tables in the database, system administration scripts, and instructions.

System Security

To accommodate the sensitive nature of laboratory animal research, we incorporated a two-layer security system. First, the system checks the IP address of the current user's client on the Internet against a table of allowed IP ranges. If there is no match, users do not gain access to any part of the system. This is used, for example, to limit access to computers physically located within a laboratory subnet, or a university system subnet. Clients attempting to access the database from an unapproved IP address immediately find themselves redirected to an informational web page. IP address testing occurs only before login. However, the login record includes the IP address and becomes invalid

if the same user attempts to access from a different IP. The range of allowed IPs is under control of the system administrator. We also restrict access by controlling our local, laboratory network with a firewall, but future versions of SCI-Base will incorporate SSL to encrypt all information while in transit. This will be particularly valuable when we implement database consolidation to allow meta-analyses of data from many sites.

The second level of security is to require a valid login name and password before access. Again, the system stores user and password data in a table in the database, where it is easily modified by the administrator. Once the user completes the login step, a security token is registered on the server along with the user identity and this token is passed from web page to web page. Most entries in the database also passively record the user for validation of data. The token is made inactive once the user logs out. This prevents unauthorized access from an open web browser by using the "back" button to refresh a web page. Should users close their browser without logging out, there are two mechanisms for clearing the expired login. On re-login, the previous login records are automatically closed. A scheduled script also clears any open logins each night. Upon each new request for data from the server, the system checks the security codes. Any time the security system is not satisfied that the user or the IP address is authorized, it disables the server record and allows no further access.

Administration

The administration subsystem appears on menus only if the user is registered as an administrator or a Principal Investigator (PI). Each user receives one or more access levels depending on the features required. The administrator or a PI can grant or revoke the access level at any time.

The system stores all procedures, drugs, dosages, routes of administration, species, strains, and other site-specific data in tables so they can be

customized easily. Administrators or PIs have access to all customizable tables and use them to create all drop-down lists to keep stored user input as uniform as possible. For example, they can add new antibiotic compounds to the drop-down list by modifying the appropriate table. Administrators and PIs can also set planned or approved dose, route, and standard concentrations as targets in the database. [Author: edits ok in previous paragraph?]

Storing Animals

A unique number, as well as an optional, user-defined tag label, identifies each animal stored. Implementation of the animal number can be with printed bar-code labels as we have done, or with implantable tracking radiofrequency IDs (RFIDs). In our Center, a standard paper mailing label is laser-printed with Code 39 label images using commercial bar-coding software (Wasp Bar Code Labeler). Because the decoding is done within the hardware of commercial bar-code scanners, the choice of codes and labels is completely outside the database system (Fig. 2). Any labeling or tagging system that reports a standard text string upon decoding would be acceptable as input. Similarly, hand entry of ID tag information is also acceptable.

Laboratories that do their own breeding

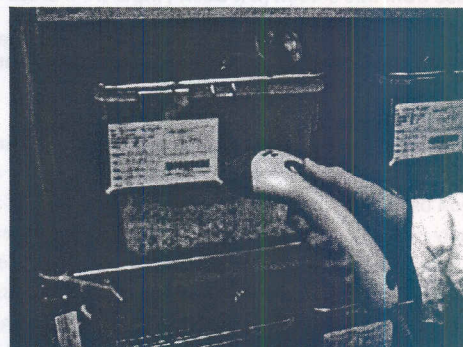


FIGURE 2. Data input using bar-coded cage cards. The user plugs a simple bar-code reader into the computer using the USB port. Care cards are printed with bar codes using commercial label-printing software (Wasp Bar Code Labeler). The reader inputs the decoded number into the animal ID field on the web page to retrieve the record for the selected animal.

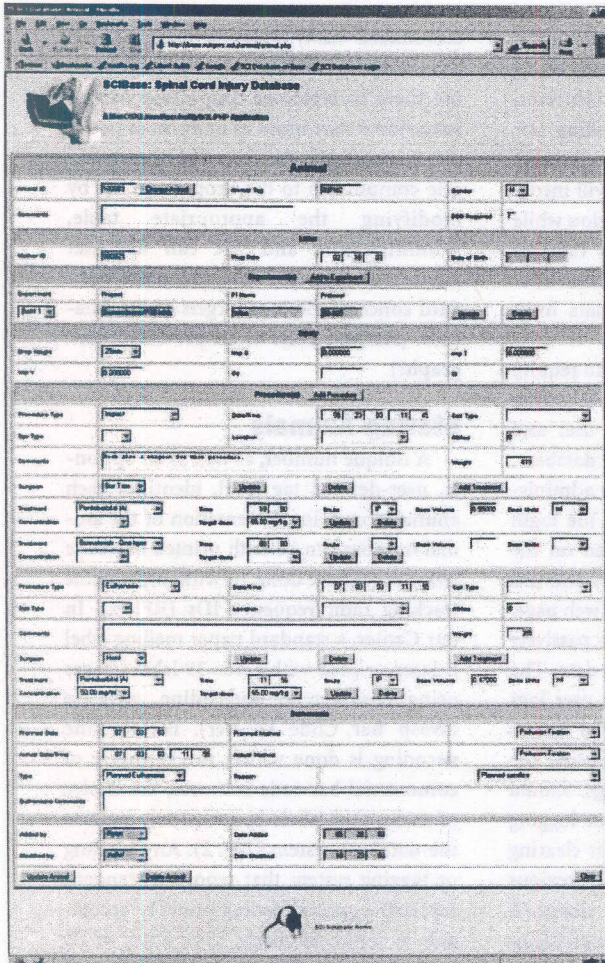


FIGURE 3. Animals page. Users can enter each animal into the database from this screen (if it wasn't input from breeding data), along with experimental procedures and treatments. The surgeon and technician identities are recorded. As needed, the euthanasia conditions as well as the reason for euthanasia are noted.

can start the process with mother and father IDs, plus a date of mating. The combination of mother ID and the mating date uniquely identify any subsequent litters. Once a litter of pups is born, the date of birth goes on record along with a count of pups. Because it is usually difficult to sex the pups until much later, one can enter a gender of 'U' (unassigned), and then update the gender assignment as needed. Generally, animals receive specific ID numbers upon weaning, and a technician affixes to the cage card a bar-coded sticker containing the animal ID.

It is possible to classify animals into experiments, and experiments into projects. Each project has a single PI and uses one or more approved IACUC protocol numbers. Animals may be members of multiple experiments. Treatment group identity is valuable in reporting data but could be a source of bias in caring for animals or in behavioral testing. Therefore animal caretakers do not have access to all group data; only PIs and administrators can see them. Although we have not yet implemented a universal switch-controlled blinding system, the database schema includes this capability. This function would hide group identifica-

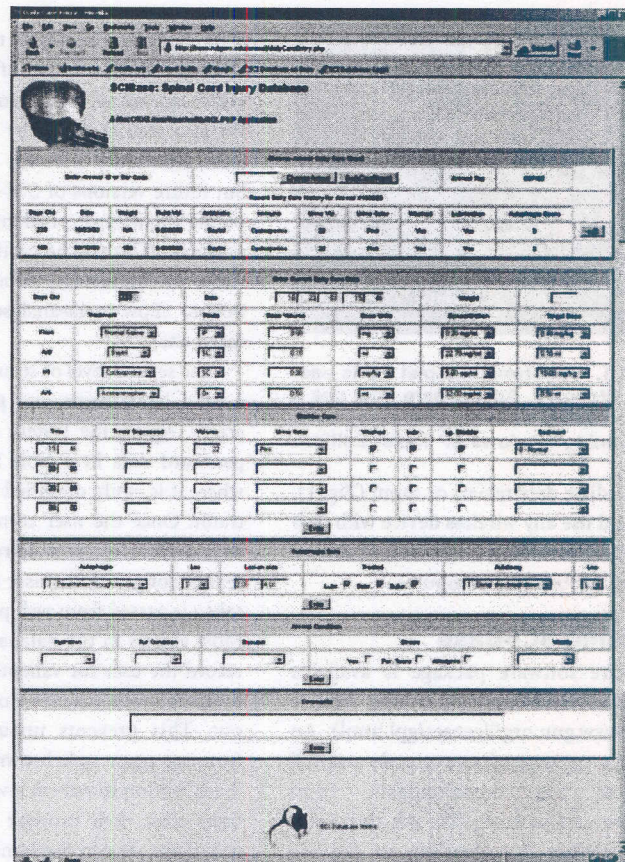


FIGURE 4. Daily care page. Caregivers enter all daily care data on this page. The system presents a short summary of the previous two observations to allow the identification of trends. Continuing treatments are pre-entered in blue text; any changes to default values change the text color to black, indicating that the source of the information has changed.

tion from all personnel until the PI actuates a switch to allow all staff to access all data.

Experimental Procedures and Treatments

We chose to group into a category called 'procedures' anything that happens to an animal, including contusion injury, cell transplants, surgical transection, tract-tracing, or any other gross surgical event. A 'treatment', in contrast, is generally a drug or biomaterial—anything that has a dose and a route of administration. A procedure can have many treatments, and animals may have multiple procedures. This structure tends to organize most of the experimental events into understandable and

Day	Day of Week	Sex	Color	Breed	Age	Status	Weight	Color	Washed	Lateral	AP/Lev	AP/HD	APV	AP/Lev
01/01/03	Thu	Y			1	1		Clear	Y	N	0.00	0.00		N
01/02/03	Fri				1	1		Clear	Y	N	0.00	0.00		N
01/03/03	Tue				2	1		Clear	N	N	0.00	0.00		N
01/04/03	Wed				2	1		Clear	N	N	0.00	0.00		N
01/05/03	Thu				2	1		Clear	N	N	0.00	0.00		N
01/06/03	Fri				2	1		Clear	N	N	0.00	0.00		N
01/07/03	Sat				1	1		Clear	N	N	0.00	0.00		N
01/08/03	Sun				1	1		Clear	N	N	0.00	0.00		N
01/09/03	Mon				2	1		Clear	N	N	0.00	0.00		N
01/10/03	Tue				1	1		Clear	N	N	0.00	0.00		N
01/11/03	Wed				1	1		Clear	N	N	0.00	0.00		N
01/12/03	Thu				1	1		Clear	N	N	0.00	0.00		N
01/13/03	Fri				2	1		Clear	N	N	0.00	0.00		N
01/14/03	Sat				1	1		Clear	N	N	0.00	0.00		N
01/15/03	Sun				1	1		Clear	N	N	0.00	0.00		N
01/16/03	Mon				0.5	1		Clear	N	N	0.00	0.00		N
01/17/03	Tue				1	1		Clear	N	N	0.00	0.00		N
01/18/03	Wed				2	1		Clear	N	N	0.00	0.00		N
01/19/03	Thu				2	1		Clear	N	N	0.00	0.00		N
01/20/03	Fri				1	1		Clear	N	N	0.00	0.00		N
01/21/03	Sat				0.5	1		Clear	N	N	0.00	0.00		N
01/22/03	Sun				1	1		Clear	N	N	0.00	0.00		N
01/23/03	Mon				2	1		Clear	N	N	0.00	0.00		N
01/24/03	Tue				0.5	1		Clear	N	N	0.00	0.00		N
01/25/03	Wed				0.5	1		Clear	N	N	0.00	0.00		N
01/26/03	Thu				1	1		Clear	N	N	0.00	0.00		N
01/27/03	Fri				0.5	1		Clear	N	N	0.00	0.00		N
01/28/03	Sat				0.5	1		Clear	N	N	0.00	0.00		N
01/29/03	Sun				1	1		Clear	N	N	0.00	0.00		N
01/30/03	Mon				0.5	1		Clear	N	N	0.00	0.00		N
01/31/03	Tue				0.5	1		Clear	N	N	0.00	0.00		N
02/01/03	Wed				1	1		Clear	N	N	0.00	0.00		N
02/02/03	Thu				0.5	1		Clear	N	N	0.00	0.00		N

FIGURE 5. Daily care report. A one-page summary tracks daily medical history. The page includes a bar code for quick access to records specific for each animal.

reportable categories.

The addition of a procedure requires recording the name of the supervising surgeon who is responsible for oversight of all treatments given as part of a procedure (Fig. 3). The administrator or a PI can grant 'surgeon' status to a user. Data entry into the animal's records also automatically stores the technician identity based on the user's login data. If the data record is modified, the record also indicates the identity of the modifier. The system also provides for a 'read-only' class of user who cannot modify or enter animal data.

Daily Care

Each animal's blank daily care record is loaded using the animal ID number, bar code, or RFID tag (Fig. 4). Simplified records from the previous two days of care are displayed so that staff can identify changes in the animal's condition. Basic daily observations and treatments are added in a simple web form, including weight, use of fluid replacement therapy, antibiotics, immunosuppressants, and analgesics. A one-page summary of all care

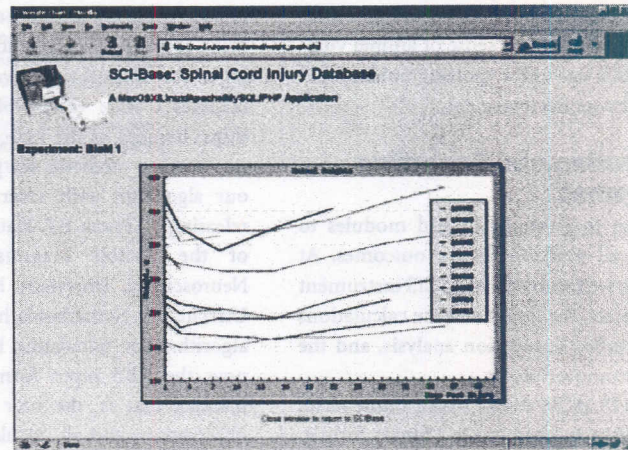


FIGURE 6. Weight graph by experiment. One quick indicator of overall animal health after a spinal contusion is the gross weight. A quick view of the change in weight over days after injury will indicate animals varying from others in the group.

can be viewed or printed at any time (Fig. 5). Our Center generally weighs animals twice a week.

Because the date of birth is known, we always calculate the age. Sudden changes in weight are often good indicators of changes in overall health of animals (Fig. 6).

For treatments, the web form seeks to guide the caretaker into the approved dose and route of administration for each drug selected. For example, selecting the antibiotic Baytril for urinary tract infection automatically displays the standard volume of injection, route, target dose, and concentration of injection solution. Using a simple client-side JavaScript routine, a change to any of the default values automatically calculates the remaining values (Fig. 4). Our goal was to guide the staff to follow prescribed protocols but also to allow for the capture of actual data, even if it deviated from our desired protocol. Supervisors have the opportunity to review daily care data and update only the most recent record if errors are detected.

Because many animals under care for paraplegia are treated identically over several days, we provide default values for selected treatments based on the previous

day's record. For example, if an animal is in the midst of a treatment course with Baytril, the form is pre-filled for the use of Baytril at the prescribed dose. To distinguish these data from staff-generated material, the automatic data are displayed in blue-colored lettering. If the user changes the values, the color changes to black to remind the careworker of the source of the data. We plan to implement a system to extend the use of these treatment defaults to display as prescribed, and then stop displaying when the course is completed.

During the first few weeks after contusion, care staff manually express bladders. They usually do this twice a day, but the frequency can vary depending on many conditions. Each manipulation goes on record, along with the volume of urine collected, the condition of the urine, and the presence of sediment.

Autophagia is a complication that can lead to removal of an animal for euthanasia. Caregivers record the incidence of mild autophagia and grade it; animals receive analgesic therapy on the basis of these records. Daily care records note progression of symptoms, so that animals are immediately recognized if treatment does not resolve symptoms.

Finally, we assess the overall health of the animal by general features such as

